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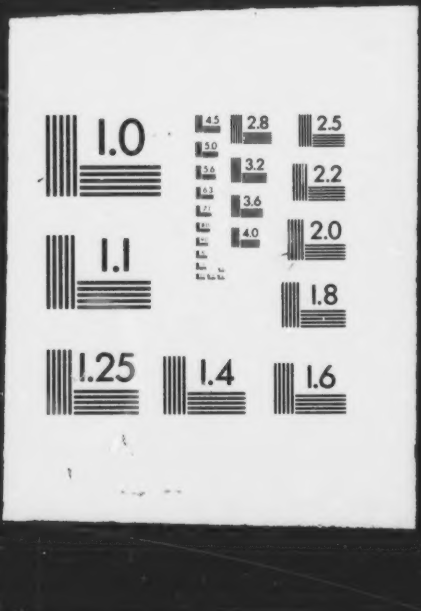
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PB88-245931

Health Advisories for 50 Pesticides (Including Acifluorfen, Ametryn, Ammonium Sulfamate Atrazine, Baygon, Bentazon, Bromacil, Butylate Carbaryl, Carboxin, Chloramben, Chlorothalonil Cyanazine, Dalapon, Dacthal, Diazinon, Dicamba 1,3-Dichloropropene, Dieldrin, Dimethrin, Dinoseb Diphenamid, Disulfoton, Diuron, Endothall Ethylene Thiourea, Fenamiphos, Fluometuron Fonofos, Glyphosate, Hexazinone, Maleic Hydrazide MCPA, Methomyl, Methyl Parathion, Metolachlor Metribuzin, Paraquat, Picloram, Prometon Pronamid, Propachlor, Propazine, Propham, Simazine, 2,4,5-T, Tebuthiuron, Terbacil Terbufos, and Trifluralin)

(U.S.) Environmental Protection Agency
Washington, DC

Aug 88

U.S. Department of Commerce
National Technical Information Service

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before complet

1. REPORT NO.	2. *	3. PB88-245931
4. TITLE AND SUBTITLE Health Advisories for 50 Pesticides		5. REPORT DATE August, 1988
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) U.S. Environmental Protection Agency Office of Drinking Water		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS U.S. Environmental Protection Agency Office of Drinking Water (WH-550D) 401 M Street, SW Washington, DC 20460		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

*This packet replaces PB88-113543/AS

16. ABSTRACT

These documents summarize the health effects of 50 pesticides including: acifluorfen, ametryn, ammonium sulfamate, atrazine, baygon, bentazon, bromacil, butylate, carbaryl, carboxin, chloramben, chlorothalonil, cyanazine, dalapon, dacthal, diazinon, dicamba, 1,3-dichloropropene, dieldrin, dimethrin, dinoseb, diphenamid, disulfoton, diuron, endothall, ethylene thiourea, fenamiphos, fluometuron, fonofos, glyphosate, hexazinone, maleic hydrazide, MCPA, methomyl, methyl parathion, metolachlor, metribuzin, paraquat, picloram, prometon, pronamid, propachlor, propazine, propham, simazine, 2,4,5-T, tebuthiuron, terbacil, terbufos, and trifluralin. Topics discussed include: General Information and Properties, Pharmacokinetics, Health Effects in Humans and Animals, Quantification of Toxicological Effects, Other Criteria Guidance and Standards, Analytical Methods, and Treatment Technologies.

KEY WORDS AND DOCUMENT ANALYSIS

DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Pesticides Drinking Water Health Advisory Toxicity		

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL INFORMATION SERVICE
SPRINGFIELD, VA. 22161

18. DISTRIBUTION STATEMENT Open Distribution	19. SECURITY CLASS (This Report) non-sensitive	21. NO. OF PAGES 861
	20. SECURITY CLASS (This page) non-sensitive	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

August, 1988

ACIFLUORFEN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

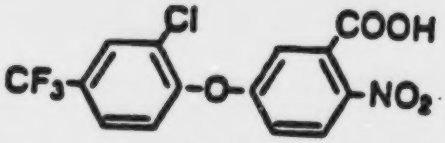
Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 5094-66-6 (acid)

62476-59-9 (sodium salt)

Structural Formula



Sodium 5-(2-chloro-4-(trifluoromethyl)-phenoxy)-2-nitrobenzoate

Synonyms

- Blazer®; Carbofluorfen; RH-6201; Tackle®; Sodium acifluorfen (Meister, 1983).

Uses

- Acifluorfen is used as a selective pre- and post-emergence herbicide to control weeds and grasses in large-seeded legumes including soybeans and peanuts (Meister, 1983).

Properties (Windholz et al., 1983; Meister, 1983; CHEMLAB, 1985; WSSA, 1983)

Chemical Formula	$C_{14}H_7ClF_3NO_5$ (acid) $C_{14}H_6ClF_3NNaO_5$ (sodium salt)
Molecular Weight	361.66 (acid) 383.65 (sodium salt)
Physical State (25°C)	Off-white solid (acid), brown crystalline powder/white powder (sodium salt)
Boiling Point	--
Melting Point	124-125°C (sodium salt) 151.5-157°C (acid)
Density	--
Vapor Pressure (25°C)	24 mm Hg (45% H_2O solution)
Specific Gravity	--
Water Solubility (25°C)	>25% (sodium salt) (dimensions not specified)
Log Octanol/Water Partition Coefficient	-4.85 (acid) (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- No information was found in the available literature on the occurrence of acifluorfen.

Environmental Fate

- Acifluorfen is stable to hydrolysis; no degradation was observed in solutions at pH 3, 6 or 9 within a 28-day interval. Varying temperatures (18 to 40°C) did not alter this stability. The half-life of the parent compound is 92 hours under continuous exposure to light approximating natural sunlight. The decarboxy derivative of acifluorfen was the primary degradate found in solution. It is suspected that a substantial percentage of the photodegradate parent is lost from solution (through volatilization or other mechanisms) (Registrtion Standard Science Chapter for Acifluorfen).

- The half-life of acifluorfen in an aerobically incubated soil was found to be about 170 days; anaerobic degradation was more rapid (half-life about 1 month). The dominant residue compounds after 6-months aerobic incubation were the parent compound and bound materials. After 2 months under anaerobic conditions, the acetamide of amino acifluorfen was the major degradate extracted from soil; the amino analog itself was also significant, and denitro acifluorfen was also formed (Registration Standard Science Chapter for Acifluorfen).

- Acifluorfen applied at 0.75 lb ai/A to a silt loam in Mississippi dissipated with a tentative half-life of 59 days. Leaching of the parent compound below 3 inches in the soil was negligible during the 179-day study. The dissipation of acifluorfen in two silt loam soils in Illinois receiving multi-residue treatments was somewhat slower; half-lives were 101 to 235 days (Registration Standard Science Chapter for Acifluorfen).

- Acifluorfen applied to soil columns at highly excessive rates indicative of spills (682 lb ai/A) is very mobile. Acifluorfen leached from the columns with 10 inches of water accounted for 79 to 93% of the acifluorfen applied. Aerobic aging of the residues in the column substantially reduced the mobility and pesticide movement was inversely proportional to the soil CEC. Results from soil TLC (un-aged residues only) predict mobility to be intermediate to mobile. Supplementary data from a batch adsorption study indicate that un-aged acifluorfen is weakly and reversibly adsorbed (Registration Standard Science Chapter for Acifluorfen).

- Greenhouse studies have demonstrated that the uptake of acifluorfen by rotational crops decreases with aging of residues in soil (Registration Standard Science Chapter for Acifluorfen).

III. PHARMACOKINETICS

Absorption

- No information was found in the available literature on the absorption of acifluorfen.

Distribution

- No information was found in the available literature on the distribution of acifluorfen.

Metabolism

- No information was found in the available literature on the metabolism of acifluorfen.

Excretion

- No information was found in the available literature on the excretion of acifluorfen.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of acifluorfen in humans.

Animals

Short-term Exposure

- The Whittaker Corporation (no date, a) reported that the oral LD_{50} of Tackle 2S (a formulation containing 20.2% sodium acifluorfen) in the rat (strain not specified) was 2,025 mg/kg for males and 1,370 mg/kg for females.

- Meister (1983) reported that the acute dermal LD_{50} of Blazer® (technical grade, purity unspecified) in the rabbit is 450 mg/kg. The acute dermal LD_{50} of Tackle® (purity unspecified) in the rabbit is 2,000 mg/kg.

- Goldenthal et al. (1978a) presented the results of a two-week range-finding study in which RH 6201 (a formulation containing 39.4% sodium acifluorfen) was administered to Charles River CD-1 mice (10/sex/dose) at dietary concentrations of 0, 625, 1,250, 2,500, 5,000 or 10,000 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these doses correspond to about 0, 93.8, 187.5, 375.0, 750.0 or 1,500 mg/kg/day. No changes in general behavior or appearance were reported at any dose level. During the second week of the study, there was a decrease in body weight and food consumption in animals receiving 10,000 ppm (1,500 mg/kg/day). Gross pathological findings included pale kidneys, yellowish livers and reddish foci of hyperemia in the stomachs of several mice at the 5,000- and 10,000-ppm (750 and 1,500 mg/kg/day) dose levels. Absolute liver weight was increased in all test groups dosed at levels of 2,500 ppm (375 mg/kg/day) or greater. The increases were statistically significant ($p < 0.01$). A statistically significant ($p < 0.01$) increase in relative liver weight was reported at all dose levels. Based on the results of this study, a Lowest-Observed-Adverse-Effect Level (LOAEL) of 625 ppm (93.8 mg/kg/day) was identified.

- Piccirillo and Robbins (1976) administered RH 6201 (a formulation containing 39.8% sodium acifluorfen) to Wistar rats (5/sex/dose) for 4 weeks at dietary concentrations of 0, 5, 50, 500 or 5,000 ppm (reported to be equivalent to 0, 0.7, 7.6, 55.4 or 506.4 mg/kg/day for males and 0, 0.8, 8.3, 60.6 or 528.2 mg/kg/day for females). Assuming that these dietary levels reflect the concentration of the test compound and not the active ingredient, corresponding levels of sodium acifluorfen are 0, 0.3, 3.0, 22.1 and 201.6 mg/kg/day for males and 0, 0.3, 3.3, 24.0 and 210.2 mg/kg/day for females (Lehman, 1959). Results of the study indicated that body weight was decreased in males at 22.1 and 201.6 mg/kg/day, and food consumption was decreased in both males at 201.6 mg/kg/day and females at 210.2 mg/kg/day. Biochemical analyses revealed that serum glutamic pyruvic transaminase (SGPT) levels were increased in males at 22.1 and 201.6 mg/kg/day; in males that received 201.6 mg/kg/day, blood urea nitrogen (BUN) was increased and glucose levels were decreased. Changes in organ weights included increased absolute liver and kidney weights in males at 201.6 mg/kg/day, increased relative liver and kidney weights in males at 201.6 mg/kg/day and females at 210.2 mg/kg/day and increased relative liver weight in males only at 22.1 mg/kg/day. Based on the results of this study, a No-Observed-Adverse-Effect Level (NOAEL) of 3.0 mg/kg/day was identified.

Dermal/Ocular Effects

- In a dermal irritation study (Whittaker Corp., no date, b), Tackle 2S (a formulation containing 20.2% sodium acifluorfen) was applied occlusively (dose not specified) to the intact and abraded skin of rabbits. Effects observed included slight erythema, slight edema, blanching of the skin, and eschar formation. Signs of dermal irritation at intact and abraded sites were absent by 8 days post-application. The test substance was considered to be a moderate dermal irritant at 72 hours.

- In a dermal irritation study, Weatherholtz et al. (1979b) applied RH 6201 (sodium acifluorfen) to the skin of New Zealand White rabbits (five/sex/dose; ten/sex/control). Three different formulations of RH 6201 were used in the study and each formulation was tested at 1.0 or 4.0 mL/kg/day. The authors indicated that for all RH 6201 formulations tested, the dose levels correspond to 50 or 200 mg/kg/day of the active ingredient. The test material was applied once daily for 5 days, followed by 2 days with no applications, over a 4-week period (total of 20 applications). At both dose levels, two of the formulations produced slight to well-defined irritation. At 200 mg/kg/day, central nervous system depression and a statistically significant decrease in body weight gain and food consumption were noted. The third formulation produced essentially the same effects, with the addition of "thinness," ataxia, slight tremors and mortality (2/5 males). Microscopic evaluations revealed chronic dermatitis, acanthosis and hyperkeratosis at both dose levels for all formulations.

- Madison et al. (1981) presented the results of the Buhler test for dermal sensitization in Hartley-derived albino guinea pigs. In this study, Tackle® (sodium acifluorfen; purity not specified) was not found to be a sensitizer when applied topically at a dose of 0.25 mL under occlusive binding.

- In an ocular irritation study (Whittaker Corp., no date, c), Tackle 2S (a formulation containing 20.3% sodium acifluorfen) was instilled into the eyes of rabbits. Signs of ocular irritation and lesions included opacities of the cornea, iritis, redness and chemosis of the conjunctiva and discharges from both washed and unwashed eyes. Four of six unwashed eyes and one of three washed eyes exhibited blistering of the conjunctiva. Three of six unwashed and one of three washed eyes exhibited pannus where corneal opacity had been.

- In an ocular irritation study (Weatherholtz et al., 1979a), 0.1 mL of Blazer 2S (purity not specified) was applied to the corneal surface of the eyes of rhesus monkeys. Corneal opacity and conjunctival redness, swelling and discharge were observed in both washed and unwashed eyes. All treated eyes were free of signs of irritation by 14 days posttreatment.

Long-term Exposure

- Harris et al. (1978) administered RH 6201 (a formulation containing 39.4% sodium acifluorfen) in the diet to Sprague-Dawley rats (15/sex/dose) for 3 months at dose levels of 0, 75, 150 or 300 mg/kg/day. Assuming that these doses reflect levels of the test compound and not the active ingredient, corresponding levels of sodium acifluorfen would be 0, 29.6, 59.1 or 118.2 mg/kg/day. At the highest dose level (118.2 mg/kg/day), a number of effects were observed in male rats. These effects included decreased body weight (13%) and decreased food consumption (8%). Biochemical analyses of blood revealed increased alkaline phosphatase levels (32%), decreased total protein (8%) and decreased albumin (14%). No such effects were reported for female rats. (These biochemical analyses were performed on control and high-dose animals only.) Increased liver weight and microscopic liver changes (enlarged hepatocytes) were observed in male rats that received 59.1 or 118.2 mg/kg/day. In terms of the active ingredient, a NOAEL of 29.6 mg/kg/day was identified.

- Barnett (1982) administered Tackle 2S (a formulation containing 20.4 to 23.6% sodium acifluorfen) to Fischer 344 rats (30/sex/dose) for 90 days at dietary concentrations of 0, 20, 80, 320, 1,250, 2,500 or 5,000 ppm. The author indicated that these dietary levels correspond to average compound intake levels of 0, 1.5, 6.1, 23.7, 92.5, 191.8 or 401.7 mg/kg/day for males and 0, 1.8, 7.4, 29.7, 116.0, 237.1 or 441.8 mg/kg/day for females. Assuming that these levels reflect test compound and not active ingredient intake, corresponding levels of sodium acifluorfen intake are approximately 0, 0.4, 1.4, 5.6, 21.8, 45.3 or 94.8 mg/kg/day for males and 0, 0.4, 1.8, 7.0, 27.4, 56.0 or 104.3 mg/kg/day for females (based on 23.6% active ingredient in test compound). At 5,000 ppm the following effects were observed: decreased body weight and food consumption in both sexes; decreased red blood cell (RBC) count, hemoglobin and hematocrit in both sexes; increased serum cholesterol and serum calcium, and decreased serum phosphorous in both sexes; increased alkaline phosphatase, SGPT and BUN levels in males; elevated urobilinogen in both sexes; increased liver size and discolored liver and kidneys in both sexes; and liver cell hypertrophy and increases in mitotic figures and individual cell deaths in both sexes. At 2,500 ppm the following effects were observed: decreased body weight in males; decreased RBC count, hemoglobin and hematocrit in both sexes; increased BUN levels in males; elevated urobilinogen in both sexes; increased liver size in both sexes; and liver cell hypertrophy and increases in mitotic figures and individual cell deaths in both sexes. At 1,250 ppm, the following effects were observed: increased liver size in males and liver cell hypertrophy in both sexes. The author identified 320 ppm as the NOAEL in this study. In terms of active ingredient concentration, this corresponds to a NOAEL of 5.6 mg/kg/day for males and 7.0 mg/kg/day for females.

- Mobil (1981) presented the 6-month interim results of a longer-term study in which Tackle 2S (a formulation containing approximately 75% sodium acifluorfen) was administered to beagle dogs (eight/sex/dose) at dietary concentrations of 0, 20, 320 or 4,500 ppm. These dietary levels were reported to be equivalent to 0, 0.7, 9.0 or 160 mg/kg/day. Assuming that these levels reflect test compound and not active ingredient intake, corresponding levels of sodium acifluorfen intake are 0, 0.5, 6.8 or 120.0 mg/kg/day (based on 75% active ingredient in the test compound). Following six months of compound administration, two animals/sex/dose were sacrificed. The study reported a number of effects at the highest dose tested. These effects included decreased body weight and food consumption and increased liver weight in both sexes. Additionally, RBC count and hemoglobin concentration were decreased in both sexes. Clinical chemistry analyses revealed depressed serum cholesterol, increased alkaline phosphatase, and transient elevation of BUN in both sexes. Males only showed increased levels of lactic dehydrogenase. No histopathological examinations were conducted. The NOAEL reported in this study was 320 ppm. In terms of the active ingredient, this corresponds to a NOAEL of 6.8 mg/kg/day.

- Barnett et al. (1982b) administered Tackle 2S (a formulation containing 19.1 to 25.6% sodium acifluorfen) to Fischer 344 rats (73/sex/dose) for 1 year at dietary levels of 0, 25, 150, 500, 2,500 or 5,000 ppm. Assuming that these dietary levels reflect the concentrations of the test compound and not the active ingredient, corresponding levels of sodium acifluorfen are 0, 6.4, 38.4, 128.0, 640.0 or 1,280 ppm (based on 25.6% active ingredient in the test compound). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, these levels correspond approximately to 0, 0.3, 1.9, 6.4, 32.0 or 64.0 mg/kg/day (Lehman, 1959). No excess moribundity or mortality was associated with the ingestion of the test substance. At 5,000 ppm, the following effects were observed: decreased mean body weight in both sexes; increased absolute and relative liver weight in both sexes; decreased protein production, decreased serum glucose, decreased triglyceride levels, increased alkaline phosphatase and creatine phosphokinase levels, and sporadic increases in SGOT and SGPT in both sexes; a slight increase in the excretion of urobilinogen in both sexes; and the presence of acidophilic cells that were considered to be evidence of cytotoxic changes in the livers of both sexes. At 2,500 ppm, male rats showed increased absolute and relative liver weights. Based on the information presented in this study, a NOAEL of 500 ppm was identified for the test compound. In terms of the active ingredient, this corresponds to a NOAEL of 6.4 mg/kg/day.

- Spicer et al. (1983) administered Tackle 2S (a formulation containing 74.5 to 82.8% sodium acifluorfen) to beagle dogs (eight/sex/dose) for 2 years at dietary concentrations of 0, 20, 300 or 4,500 ppm, reported to be equivalent to 0, 0.5, 7.3 or 121 mg/kg/day for males and 0, 0.5, 8.3 or 154 mg/kg/day for females. Assuming that these dietary levels reflect the concentration of the test compound and not the active ingredient, corresponding levels of sodium acifluorfen are 0, 0.4, 6.0 or 100.2 mg/kg/day for males and 0, 0.4, 6.9 or 127.5 mg/kg/day for females (based on 82.8% active ingredient in the test compound). At the highest dose, body weight was decreased (not statistically significant), and a corresponding (statistically significant) decrease in food consumption was also reported. Physical examination revealed heart anomalies in the high- and mid-dose groups. At the high dose, irregular heart rhythms and rapid or slow heart rates were reported in one male and four females. Also at this dose level, one male was found to have a systolic murmur. At the mid-dose level, one animal of each sex had an irregular heart rhythm (accompanied by rapid heart rate in the male). At the highest dose tested, a number of changes were reported, including a statistically significant decrease in erythrocyte count, hemoglobin and hematocrit in both sexes; reductions in albumin and cholesterol; increased absolute and relative liver and kidney weights; and histopathological liver changes including centrilobular hepatocellular fatty vacuolation, bilirubin pigmentation and minimal foci of alteration. Renal tubules showed bilirubin pigmentation at all dose levels (most pronounced at the high dose). The authors concluded that this study showed clear evidence of target organ toxicity affecting the liver and possibly the kidney at the highest dose level. The authors identified 300 ppm (of test compound) as the NOAEL. In terms of the active ingredient, this corresponds to a NOAEL of 6.0 mg/kg/day.

- Goldenthal (1979) administered RH 6201 (a formulation containing 39.4 to 40.5% sodium acifluorfen) to Charles River CD-1 mice (80/sex/dose) for two years in the diet at concentrations that provided dosage levels of 0, 1.25, 7.5 or 45.0 ppm of the active ingredient. After 16 weeks of administration, the 1.25 ppm dose was increased to 270 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day, these levels correspond to about 0, 0.19 (increased to 40.5), 1.13 and 6.8 mg/kg/day (Lehman, 1959). Two control groups were used in this study. One group received acetone in the diet (control 1), and the other received water in the diet (control 2). At the 40.5 mg/kg/day dose level, the following effects were observed: slight to marked elevations in alkaline phosphatase and SGPT levels, in both sexes, beginning after one year of exposure; increased absolute and relative liver weight in males; increased absolute liver weight in females; increased relative kidney weight in males; decreased absolute heart weight in males; cellular alterations in the livers of males consisting of focal pigmentation, focal hepatocytic necrosis, focal cellular alteration, nodular hepatocellular proliferation and hepatocellular carcinoma (the only statistically significant change was the focal cellular alteration); and focal pigmentation in the livers of females. At the 6.8 mg/kg/day dose level, the following effects were observed: occasional increases in alkaline phosphatase and SGPT levels in both sexes; decreased absolute heart weight in males; and focal pigmentation in the livers of females. The author indicated that changes with an apparent dose-related distribution included focal pigmentation, hepatocellular vacuolation, focal hepatocytic necrosis and nodular hepatocellular proliferation. The incidence of hepatocellular carcinoma in males of all treatment groups was approximately the same. A NOAEL of 7.5 ppm (1.13 mg/kg/day) was identified by the author.

Reproductive Effects

- In a three-generation reproduction study, Goldenthal et al. (1978b) administered RH 6201 (a formulation containing sodium acifluorfen) in the diet to Charles River CD rats. During the course of the study, the test compound was administered at various levels depending on the age of the animals. The F_1 generation received dose levels of 2.9, 17.3 or 104 ppm during the first 2 weeks of the study, and 5, 30 and 180 ppm for the remaining weeks of the generation (study weeks 3 to 17) (Time-Weighted Average (TWA) dosage levels 4.8, 28.5 or 171.1 pm). The F_2 and F_3 generations received dosage levels of 180, 10 or 60 ppm during the first and second weeks of the generation; 312, 17.3 or 104 ppm during the third, fourth and fifth weeks of the generation; and 540, 30 or 180 ppm for the remaining weeks of the generation (TWA for F_2 generation 486.0, 27.0 or 162.0 ppm; TWA for F_3 generation 483.8, 26.7 or 161.3 ppm). The highest dietary TWA dose tested in this study was 486 ppm of active ingredient. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, this corresponds to a dose of 24.3 mg/kg/day (Lehman, 1959). No effects related to compound administration were observed in parents or pups in terms of general behavior, appearance or survival. Parental and pup body weights and food consumption were similar to controls. Fertility, gestation and viability indices were comparable for controls and treated groups. There were no biologically meaningful teratogenic effects in the second or third generation, based on mean number of viable fetuses, post-implantation losses, total implantations and corpora lutea per dam, mean fetal body weight, number of fetal anomalies and sex-ratio variations. No compound-related gross lesions were noted in third-generation pups necropsied. Based on the information presented, a NOAEL of 486 ppm (24.3 mg/kg/day) was identified. This NOAEL represents the highest dose tested.

- In a two-generation reproduction study, Lochry et al. (1986) administered technical grade Tackle (sodium acifluorfen) of unspecified purity to rats at levels of 0, 25, 500 and 2,500 ppm. The compound was administered in the diet ad libitum to groups of 35 rats/sex/dose beginning at 47 days of age and continuing until sacrifice. In addition, the compound was also administered to groups of 40 rats/sex/dose from weaning until sacrifice. Reproductive paramaters, mortality, body weight and a number of other end points were measured; in addition, both gross and histopathological examinations were conducted. The NOAEL for toxicity to both the parents and offspring was 25 ppm, based on mortality and kidney lesions at higher doses. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, the NOAEL of 25 ppm in this study corresponds to 1.25 mg/kg/day (Lehman, 1959).

Developmental Effects

- Lightkep et al. (1980) administered Tackle 2S (a formulation containing 22.4% sodium acifluorfen) by oral intubation at doses of 0, 3, 12 or 36 mg/kg/day to New Zealand White rabbits (16/dose) on days 6 to 29 of gestation. The authors indicated that the administered doses were in terms of the active ingredient. At 36 mg/kg/day, there was a slight (nonsignificant) inhibition of maternal body weight gain and a marked (significant) inhibition of maternal food consumption. At this dose level, there was also possible interference with implantation and a slight decrease in average fetal body weight; neither of these changes was statistically significant. No gross, soft-tissue or skeletal malformations were observed in pups, fetuses or late resorptions at any dose level. Based on the information presented in this study, a NOAEL of 36 mg/kg/day was identified for maternal toxicity, fetal toxicity and teratogenicity. This NOAEL represents the highest dose tested.

- Florek et al. (1981) administered Tackle 2S (a formulation containing 22.4% sodium acifluorfen) by gavage at doses of 0, 20, 90 or 180 mg/kg/day to Sprague-Dawley rats (25/dose) on days 6 to 19 of gestation. The authors indicated that the administered doses were in terms of active ingredient. At 180 mg/kg/day, dams gained significantly less weight than controls. At 90 and 180 mg/kg/day, lower average fetal body weight and significantly delayed ossification of metacarpals and forepaw and hindpaw phalanges were noted. At 180 mg/kg/day, there was delayed ossification of caudal vertebrae, sternebrae and metatarsals. Additionally, at the highest dose level there was a significantly increased incidence of slight dilation of the lateral ventricle of the brain. The authors stated that the fetal effects were indicative of delayed fetal development. Based on the results of this study, a NOAEL of 90 mg/kg/day for maternal toxicity, a NOAEL of 20 mg/kg/day for fetotoxicity and a NOAEL of 180 mg/kg/day (the highest dose tested) for teratogenic effects were identified.

- Weatherholtz and Piccirillo (1979) administered RH 6201 (a formulation containing 39.8% sodium acifluorfen) by gavage at doses of 0, 20, 60 or 180 mg/kg/day to New Zealand White rabbits on days 7 to 19 of gestation. Maternal toxicity at 180 mg/kg/day included statistically significant weight loss and mortality. At 180 mg/kg/day, there was also evidence of fetal toxicity (mortality). Due to embryotoxicity and maternal toxicity at 180 mg/kg/day, teratogenic evaluations could not be performed at this dose level. At lower doses, no teratogenic effects were observed. Based on the results of this study, NOAELs of 60 mg/kg/day were identified for teratogenic effects, maternal toxicity and fetal toxicity.

Mutagenicity

- Schreiner et al. (1980) tested Tackle 2S (purity unspecified) in an Ames assay using Salmonella typhimurium strains TA 98, 100, 1535, 1537 and 1538. The test compound was not found to be mutagenic, with or without metabolic activation, at concentrations up to 1.8 mg/plate.
- Brusick (1976) tested RH 6201 (purity not specified) in a mutagenicity assay using Saccharomyces cersvisiae strain D4 and S. typhimurium strains TA 1535, 1537, 1538, 98 and 100. The compound was not found to be mutagenic, with or without metabolic activation, at concentrations up to 500 ug/plate.
- Putnam et al. (1981) tested Tackle 2S (purity not specified) in a dominant lethal assay using Sprague-Dawley rats. The compound was administered by gavage at doses of 0, 80, 360 or 800 mg/kg/day for 5 consecutive days. No detectable mutagenic activity, as defined by induction of fetal death, was reported.
- Myhr and McKeon (1981) conducted a primary rat (Fischer 344) hepatocyte unscheduled DNA synthesis (UDS) assay using Tackle 2S (purity not specified). The test compound did not induce a detectable level of UDS over a concentration range of 0.10 to 25 ug/mL. Treatment of hepatocytes with 50 ug/mL was almost completely lethal to the cells.
- Schreiner et al. (1981) tested Tackle 2S (purity not specified) in a bone marrow metaphase analysis using Sprague-Dawley rats. The animals were given the test compound by intubation at doses of 0, 0.37, 1.11 or 1.87 g/kg/day for 5 days. The test compound did not significantly increase clastogenic events in the bone marrow cells.
- Schreiner et al. (1980) tested Tackle 2S (purity not specified) in a murine lymphoma assay. The compound was tested without metabolic activation at 0.11 to 1.7 ug/mL, and with metabolic activation at 0.08 to 0.56 ug/mL. No detectable mutagenic activity was detected either with or without activation.
- Jagannath (1981) tested Tackle 2S (29.7% purity) in a mitotic recombination assay using Saccharomyces cerevisiae strain D5. The compound was tested at 0, 2.5, 5.0 or 7.5 uL/plate without metabolic activation, and at 7.5, 10.0 and 25.0 uL/plate with metabolic activation. In the absence of metabolic activation, the compound induced a dose-related increase in recombination events (significant at 5.0 uL/plate). With metabolic activation, a dose of 10.0 uL/plate induced an increase in recombination events. The authors reported that very few survivors were observed at 25.0 uL/plate.

- Bowman et al. (1981) tested Tackle 2S (purity not specified) in mutagenicity assays using Drosophila melanogaster. Assays included the Biothorax test of Lewis, a dominant lethal assay, an assay for Y-chromosome loss, and a White Ivory reversion assay. In all cases, the test compound was tested at concentrations of 15 mg/mL. Results of these assays were negative for somatic reversions of White Ivory and the Biothorax test of Lewis and positive for Y-chromosome loss and dominant lethal mutations.

Carcinogenicity

- Barnett et al. (1982b) administered Tackle 2S (a formulation containing 19.1 to 25.6% sodium acifluorfen) to Fischer 344 rats (73/sex/dose) for one year at dietary levels of 0, 25, 150, 500, 2,500 or 5,000 ppm. Assuming that these dietary levels reflect the concentrations of the test compound and not the active ingredient, corresponding levels of sodium acifluorfen are 0, 6.4, 38.4, 128.0, 640.0 or 1,280 ppm (based on 25.6% active ingredient in the test compound). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, these doses correspond to approximately to 0, 0.3, 1.9, 6.4, 32.0 or 64.0 mg/kg/day (Lehman, 1959). Histopathological examinations revealed no evidence of carcinogenicity at any dose level.

- Barnett et al. (1982a) administered Tackle® (a formulation containing 24% sodium acifluorfen) to $B6C3F_1$ mice (60/sex/dose) for 18 months at dietary concentrations of 0, 625, 1,250 or 2,500 ppm. (The high dose was reported to be the maximum tolerated dose.) The authors reported that the dietary levels corresponded to average compound intake values of 0, 118.96, 258.73 or 655.15 mg/kg/day for males, and 0, 142.50, 312.65 or 710.54 mg/kg/day for females. Assuming that these levels reflect test compound and not active ingredient intake, corresponding levels of sodium acifluorfen intake are 0, 28.55, 62.10 or 157.24 mg/kg/day for males and 0, 34.20, 75.04 or 170.53 mg/kg/day for females. An obvious dose-related depression of body weight was reported for all doses. Beginning in week 52 of the study and continuing with increasing frequency was the appearance of palpable abdominal masses. Gross necropsy revealed a dose-related increase in liver masses in both sexes. Histopathological examinations conducted at the 52-week interval revealed that the livers of six animals per sex of high-dose animals (157.24 mg/kg/day for males; 170.53 mg/kg/day for females) showed evidence of acidophilic cells. Males receiving this dose displayed a statistically significant increase in the frequency of hepatocellular adenomas. After 18 months of treatment, all 40 high-dose males and 27/47 high-dose females sacrificed were found to have a single benign hepatoma, multiple benign hepatomas or hepatocellular carcinomas. In the males, the incidence of single benign hepatoma and hepatocellular carcinomas was statistically significant. In the females, the incidence of single hepatomas was statistically significant.

- Goldenthal (1979) administered RH 6201 (a formulation containing 39.4 to 40.5% sodium acifluorfen) to Charles River CD-1 mice (80/sex/dose) for two years in the diet at concentrations that provided dose levels of 0, 1.25, 7.5 or 45.0 ppm of the active ingredient. After 16 weeks of administration, the 1.25 ppm dose was increased to 270 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day, these doses correspond to approximately 0, 0.19 (increased to 40.5), 1.13 or 6.8 mg/kg/day (Lehman, 1959). Two control groups were used in this study. One group received acetone in the diet (control 1) and the other received water in the diet (control 2). In males receiving the highest dose there was a nonstatistically significant increase in the incidence of nodular hepatocellular proliferation and hepatocellular carcinoma, which indicated to the authors that these changes were dose-related.

- Coleman et al. (1978) administered RH 6201 (a formulation containing 39.8% sodium acifluorfen) to Charles River Outbred albino CD COBS rats (approximately 75/sex/dose) for 2 years at changing dietary concentrations. Mean sodium acifluorfen intake values over the course of the study were 0, 1.25, 7.54 and 17.56 mg/kg/day for males and 0, 1.64, 9.84 and 25.03 mg/kg/day for females.
- Acifluorfen is structurally similar to nitrofen [2,4-dichloro-1-(4-nitrophenoxy) benzene; CAS No. 1836-75-7]. Nitrofen has been shown to be carcinogenic in Osborne-Mendel rats and B6C3F1 mice (NCI, 1978, 1979; both as cited in NAS, 1985).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\underline{\quad}\ \text{L/day})} = \underline{\quad}\ \text{mg/L}\ (\underline{\quad}\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were found in the available literature that were suitable for determination of a One-day HA value for acifluorfen. It is therefore recommended that the Ten-day HA value for a 10-kg child (2 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Florek et al. (1981) has been selected to serve as the basis for determination of the Ten-day HA for a 10-kg child. In this study, Tackle 2S (a formulation containing 22.4% sodium acifluorfen) was administered by gavage at doses of 0, 20, 90 or 180 mg/kg/day to Sprague-Dawley rats (25/dose) on days 6 to 19 of gestation. The authors indicated that the administered doses were in terms of active ingredient. At 180 mg/kg/day, dams reportedly gained significantly less weight than controls. At 90 and 180 mg/kg/day, lower average fetal body weight and significantly delayed ossification of metacarpals and forepaw and hindpaw phalanges were noted. At 180 mg/kg/day, there was delayed ossification of caudal vertebrae, sternebrae and metatarsals. Additionally, at the highest dose level there was a significantly increased incidence of slight dilation of the lateral ventricle of the brain. The authors stated that the fetal effects were indicative of delayed fetal development. No effects on implantations, litter size, fetal viability, resorption or fetal sex ratio were reported. Based on the results of this study, a NOAEL of 20 mg/kg/day for fetotoxicity was identified.

The Ten-day HA for the 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(20\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 2\ \text{mg/L}\ (2{,}000\ \text{ug/L})$$

where:

20 mg/kg/day = NOAEL, based on absence of fetal toxicity in rats exposed to acifluorfen via gavage during days 6 to 19 of gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The study by Barnett (1982) had been selected to serve as the basis for determination of the Longer-term HA. In this study, the NOAEL was 5.6 mg/kg/day based on an increase in the size of the liver in male rats. However, a lower NOAEL, 1.25 mg/kg/day, was recently identified in a two-generation rat reproduction study by Lochry et al. (1986). Since the NOAEL in the Lochry et al. (1986) study is numerically identical to the value on which the DWEL is based and since a two-generation reproduction study is suitable for calculating a Longer-term HA, it was determined that it is appropriate to base the Longer-term HA on the DWEL.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.25\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.13\ \text{mg/L}\ (100\ \text{ug/L})$$

where:

1.25 mg/kg/day = NOAEL (see Lifetime Health Advisory below).

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.25\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 0.44\ \text{mg/L}\ (400\ \text{ug/L})$$

where:

1.25 mg/kg/day = NOAEL (see Lifetime Health Advisory below).

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur.

The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

A 2-year Charles River CD-1 mouse dietary study by Goldenthal (1979) was originally selected to serve as the basis for determination of the DWEL for acifluorfen. In this study, a NOAEL of 1.13 mg/kg/day was identified. More recently, however, a two-generation rat reproduction study by Lochry et al. (1986) was identified that strongly supports the results of the Goldenthal (1979) study and identifies a NOAEL of 1.25 mg/kg/day.

Using the NOAEL of 1.25 mg/kg/day, the DWEL for acifluorfen is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(1.25\ \text{mg/kg/day})}{(100)} = 0.013\ \text{mg/kg/day}$$

where:

1.25 mg/kg/day = NOAEL, based on the absence of mortality and kidney lesions in rats.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.013\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.437\ \text{mg/L}\ (400\ \text{ug/L})$$

where:

0.013 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Acifluorfen may be classified in Group B2: probable human carcinogen. A Lifetime HA is not recommended for acifluorfen. The estimated excess cancer risk associated with lifetime exposure to drinking water containing acifluorfen at 437 ug/L is approximately 4×10^{-4} (4.4×10^{-4}). This estimate represents the upper 95% confidence limit from extrapolations (U.S. EPA, 1988) prepared by using the Weibull 82 multistage model (time to death).

Evaluation of Carcinogenic Potential

- Four studies that evaluated the carcinogenic potential of sodium acifluorfen were identified. The results of one of these studies (Barnett et al., 1982a) indicated that sodium acifluorfen was carcinogenic in B6C3F$_1$ mice. The results of the other three studies (Goldenthal, 1979; Coleman et al., 1978; Barnett et al., 1982b) provided no evidence of carcinogenicity in two strains of rats and one strain of mice. However, due to deficiencies in the three negative studies, the results of these studies are not sufficient to contradict the results of the positive study. Each of these studies is discussed briefly below.

  - In the positive study (Barnett et al., 1982a), B6C3F$_1$ mice received sodium acifluorfen in the diet for 18 months. At the end of the study, the high-dose (157.24 mg/kg/day) male mice displayed a statistically significant increase in the incidence of single benign hepatomas and hepatocellular carcinomas. A statistically significant increase in the incidence of single hepatomas was observed in high-dose (170.53 mg/kg/day) females.

  - In one of the studies with negative results (Goldenthal, 1979) Charles River CD-1 mice received sodium acifluorfen in the diet for two years at doses of 0, 0.19 (increased to 40.5 after 16 weeks), 1.13 or 6.8 mg/kg/day. Although no evidence of carcinogenicity was observed in this study, the dose levels tested were considerably lower than the level that produced positive results in the 18-month mouse feeding study (157.24 mg/kg/day) (Barnett et al., 1982a).

  - In the second study with negative results (Coleman et al., 1978), Charles River outbred albino CD COBS rats received sodium acifluorfen for two years at dietary levels up to 25.03 mg/kg/day (females) or 17.56 mg/kg/day (males). Although it is difficult to make cross-species comparisons, these levels are considerably lower than the level that produced positive results in the 18-month mouse feeding study (157.24 mg/kg/day) (Barnett et al., 1982a). In addition, no adverse effects were observed at any dose level used in this study, indicating that the maximum tolerated dose was not used.

  - In the third study with negative results (Barnett et al., 1982b), Fischer 344 rats received sodium acifluorfen for 1 year at dietary concentrations of 0, 0.3, 1.9, 6.4, 32.0 or 64.0 mg/kg/day. Although the results of this study were negative, a study duration of 1 year is not sufficient for assessing carcinogenic potential.

- Acifluorfen is structurally similar to nitrofen [2,4-dichloro-1-(4-nitrophenoxy) benzene; CAS No. 1836-75-7]. Nitrofen has been shown to be carcinogenic in Osborne-Mendel rats and B6C3F$_1$ mice [NCI, 1978, 1979; both as cited in NAS (1985)]. Although data on nitrofen cannot be used to conclude that sodium acifluorfen is carcinogenic, these data do, to some extent, support the positive results of Barnett et al. (1982a).

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of acifluorfen.
- Evidence has been presented in one carcinogenicity study (Barnett et al., 1982a) showing that acifluorfen is carcinogenic to mice. Using the Weibull 82 increased multistage time-to-death with tumor model (since there is a survival disparity for male mice), the U.S. EPA (1988) reported a unit risk, q_1*, estimated in human equivalent (surface area conversion) as 3.55×10^{-2} $(mg/kg/day)^{-1}$ [B_2]. It was noted that q_1* is an estimate of upper (95%) bound on risk and the true value of risk is unknown and may be as low as zero.
- Using this q_1* value and assuming that a 70-kg human adult consumes 2 liters of water a day over a 70-year lifespan, the Weibull 82 multistage model estimates that concentrations of 100, 10 and 1 ug acifluorfen per liter may result in excess cancer risk of 10^{-4}, 10^{-5} and 10^{-6}, respectively.
- For comparison purposes drinking water concentrations associated with an excess risk of 10^{-6} were 0.2 ug/L, 0.7 ug/L, 7 ug/L, <0.002 ug/L and <0.002 ug/L for the multihit, one-hit, probit, logit and Weibull models, respectively.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), acifluorfen is classified in Group B2: probable human carcinogen.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA has established residue tolerances for sodium acifluorfen in or on raw agricultural commodities that range from 0.01 to 0.1 ppm (CFR, 1985).
- The EPA RfD Workgroup has concluded that an RfD of 0.013 mg/kg/day is appropriate for acifluorfen.

VII. ANALYTICAL METHODS

- Analysis of acifluorfen is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated acid pesticides in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is acidified. The compounds are extracted with ethyl ether using a separatory funnel. The derivatives are hydrolyzed with potassium hydroxide, and extraneous organic material is removed by a solvent wash. After acidification, the acids are extracted and converted to their methyl esters using diazomethane as the derivatizing agent. Excess reagent is removed, and the esters are determined by electron capture GC. The method detection limit has not been determined for this compound, but it is estimated that the detection limits for analytes included in this method are in the range of 0.5 to 2 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Reverse osmosis (RO) is a promising treatment method for pesticide-contaminated water. As a general rule, organic compounds with molecular weights greater than 100 are candidates for removal by RO. Larson et al. (1980) report 99% removal efficiency of chlorinated pesticides by a thin-film composite polyamide membrane operating at a maximum pressure of 1,000 psi and at a maximum temperature of 113°F. More operational data are required, however, to specifically determine the effectiveness and feasibility of applying RO for the removal of acifluorfen from water. Also, membrane adsorption must be considered when evaluating RO performance in the treatment of acifluorfen-contaminated drinking water supplies.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

AMETRYN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

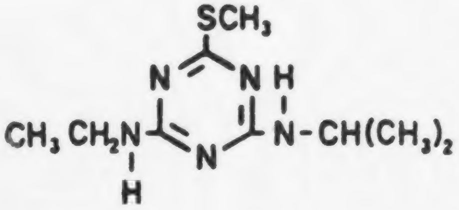
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 834-12-8

Structural Formula



2-(Ethylamino)-4-(isopropylamino)-6-(methylthio)-s-triazine

Synonyms

- N-ethyl-N'-(1-methylethyl)-6-(methylthio)-1,3,5-triazine-2,4-diamine; Ametrex; Ametryne; Cemerin; Crisatine; Evik 80W; Gesapax (WSSA, 1983; Meister, 1983).

Uses

- A selective herbicide for control of broadleaf and grass weeds in pineapple, sugarcane, bananas and plantains. Also used as a post-directed spray in corn, as a potato vine dessicant and for total vegetation control (WSSA, 1983).

Properties (WSSA, 1983)

Chemical Formula	$C_9H_{17}N_5S$
Molecular Weight	227.35
Physical State	Colorless crystals
Boiling Point	--
Melting Point	84 to 85°C
Density	--
Vapor Pressure	8.4×10^{-7} mm Hg
Specific Gravity	--
Water Solubility	185 mg/L
Log Octanol/Water Partition Coefficient	-1.72 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Ametryn has been found in 2 of 1,190 surface water samples analyzed and in 24 of 560 ground water samples (STORET, 1988). Samples were collected at 215 surface water locations and 513 ground water locations, and ametryn was found in 6 states. The 85th percentile of all nonzero samples was 0.1 ug/L in surface water and 210 ug/L in ground water sources. The maximum concentration found was 0.1 ug/L in surface water and 450 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- In aqueous solutions, ametryn is stable to natural sunlight, with a half-life of greater than 1 week. When exposed to artificial light for 6 hours, 75% of applied ametryn remained. One photolysis product was identified as 2-ethylamino-4-hydroxy-6-isopropylaminos-triazine (Registrant CBI data).

- Ametryn is stable to photolysis on soil (Registrant CBI data).

- Soil metabolism of ametryn, under aerobic conditions, proceeds with a half-life of greater than 2 to 3 weeks. Metabolic products include 2-amino-4-isopropylamino-6-methylthio-s-triazine, 2-amino-4-ethylamino-6-methylthio-s-triazine and 2,4-diamino-6-methylthio-triazine. Under anaerobic conditions the rate of metabolism decreases ($t_{1/2}$ = 122 days) (Registrant CBI data).

- Under sterile conditions ametryn does not degrade appreciably. Therefore, microbial degradation is a major degradation pathway (Registrant CBI data).

- Neither ametryn nor its hydroxy metabolite leach past 6 in. depth with normal rainfall. However, since both compounds are persistent they may leach under exaggerated rainfall or flood and furrow irrigation. This behavior is seen with other triazines (Registrant CBI data).

- Ametryn's Freundlich soil-water partition coeficient values, Kd, range from 0.6 in sands to 5.0 in silty clay soils. Specifically, the Kd for a sandy loam is 4.8, and for 2 silty loams, 3.8 and 2.8, respectively.

- In the laboratory, Ametryn has a half-life of 36 days. In the field, Ametryn degraded with a half-life of 125 to 250 days (Registrant CBI data).

III. PHARMACOKINETICS

Absorption

- Oliver et al. (1969) administered ^{14}C-labeled ametryn orally to Sprague-Dawley rats. Investigators stated that ametryn was administered by stomach tube to animals at dosage levels from 1 to 4 mg per animal. When the label was in the ring, 32.1% was excreted in the feces, indicating that over 70% had been absorbed. When the label was in the ethyl or isopropyl side chains, only 2 to 5% was excreted in the feces.

Distribution

- Oliver et al. (1969) administered ring-labeled ametryn orally to male and female Sprague-Dawley rats and measured distribution of label in tissues at 6, 48 and 72 hours after dosing. Tissue distribution at 6 hours was greatest in kidney, followed by liver, spleen, blood, lung, fat, carcass, brain, and muscle. Blood levels remained relatively constant for 72 hours after dosing, while all other tissue levels dropped rapidly to <0.1% of dose per gram of tissue.

Metabolism

- Oliver et al. (1969) administered ^{14}C-labeled ametryn orally to groups of six male and six female Sprague-Dawley rats. When the label was in the isopropyl side chain, 41.9% of the label appeared as CO_2. When the label was in the ethyl side chain, 18.1% of the label appeared as CO_2. This indicated that the side chains were extensively metabolized. When the ring was uniformly labeled with carbon-14 and the compound fed orally to rats, 58% was excreted in the urine but it was not determined whether excretion of the original compound or metabolites had occurred.

Excretion

- Oliver et al. (1969) studied the excretion of ametryn utilizing uniformly labeled compound with ^{14}C-ametryn in the ring or in the ethyl or isopropyl side chains. Forty-eight hours after oral dosing of six male and six female Sprague-Dawley rats, 57.6% of the ring labeled activity had been excreted in the urine with 32.1% excreted in the feces (total 89.7% of dose). When the fed compound was labeled in the side chains, however, much of the ^{14}C was excreted in expired air as carbon dioxide. When fed compound labeled in the isopropyl side chain, rats excreted 41.9% of the label in expired air 20% in the urine, 2% in the feces and 7% remained in the carcass (total 70.9%) at 48 hours. When the ethyl side chain contained the label, 18.1% of the label was excreted as carbon dioxide, 45% in the urine, 5% in the feces and 9% remained in the carcass (total 77.1% of dose). After 72 hours, total recovery was approximately 88% for both of the side-chain labeled compounds.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of ametryn in humans.

Animals

Short-term Exposure

- The following acute oral LD_{50} values for ametryn in rats were reported: Charles River CD rats, 1,207 mg/kg (males), 1,453 mg/kg (females) (Grunfeld, 1981); mixed male and female rats (strain not specified), 1,750 mg/kg (Stenger and Planta, 1961a); male and female Wistar rats, 1,750 mg/kg (Consultox Laboratories Limited, 1974).

- Piccirillo (1977) reported the results of a 28-day feeding study in male and female mice. Animals were 5 weeks of age and weighed 21 to 28 g at the beginning of the study. Animals (five/sex/dose) were fed diets containing 0, 100, 300, 600, 1,000, 3,000, 10,000 or 30,000 ppm of ametryn (technical). Based on the assumption that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these doses correspond to 0, 15, 45, 90, 150, 450, 1,500 or 4,500 mg/kg/day. At 30,000 ppm in the diet, all animals died within 2 weeks. At 10,000 ppm, 3 of the 10 died within 2 weeks. No other deaths occurred at any other dose level. Clinical signs in the two highest dose groups included hunched appearance, stained fur and labored respiration. At the 3,000-ppm dose level, only 1 of the 10 animals showed clinical signs of toxicity. Body weight gain was comparable in all survivors by the end of week 4. Gross pathology in animals that died showed a dark-red mucosal lining of the gastrointestinal tract and ulcerated areas of the gastric mucosa. There was no histopathological examination of tissues in this study.

- Stenger and Planta (1961b) reported a 28-day study of the toxicity of ametryn in rats. Dose levels of 100, 250 or 500 mg/kg/day were administered 6 days/week by gavage to groups of five male and five female rats. The study indicated that there was a control group but no data were given. At the 500-mg/kg/day dose level, animals became emaciated, weight gain was limited and 7 of 10 rats died. Histopathological examination of the animals that died indicated severe vascular congestion, centrilobular liver necrosis and fatty degeneration of individual liver cells. At 250 mg/kg/day, 1 of 10 rats died during the study and there was depressed growth rate in the survivors. Histological examination of liver, kidney, spleen, pancreas, heart, lung, intestine and gonads showed no major degenerative changes. No effects were reported in animals administered 100 mg/kg/day, which was identified as the No-Observed-Adverse-Effect-Level (NOAEL) in this study.

- Ceglowski et al. (1979) administered single oral doses of 88 or 880 mg/kg of ametryn to mice 5 days before, on the day of or 2 days after immunization with sheep erythrocytes (purity not specified). All mice receiving the highest dose (880 mg/kg) of ametryn had significant depression of splenic plaque-forming cell numbers when assayed 4 days later. Animals receiving the low dose showed no effect. Similarly, animals receiving 88 mg/kg for 8 or 28 consecutive days prior to immunization exhibited no significant reduction in antibody plaque formation.

Dermal/Ocular Effects

- Two of six rabbits showed mild skin irritation when ametryn was left in contact with intact or abraded skin (500 mg/2.5 cm^2) for 24 hours (Sachsse and Ullmann, 1977).

- In a sensitization study with Perbright White guinea pigs (Sachsse and Ullmann, 1977), 10 male and 10 female guinea pigs weighing 400 to 450 g received 10 daily intracutaneous 0.1-mL injections of 0.1% ametryn in polyethylene glycol:saline (70:30). Fourteen days after the last dose, animals were challenged by an occlusive dermal application of ametryn or by an intradermal challenge. Animals showed no sensitization reaction following the dermal application of the challenge dose but there was a positive response after the intradermal challenge.

- Kopp (1975) found that ametryn (technical grade) placed in the eyes of rabbits produced slight conjunctival redness at 24 hours. This cleared completely within 72 hours.

- Sachsse and Bathe (1976) applied 2,150 mg/kg or 3,170 mg/kg ametryn in suspension to the shaved backs of five male and five female rats weighing 180 to 200 g. The occlusive covering was removed at 24 hours, the skin was washed and animals were observed for 14 days. There was no local irritation or adverse reaction, and at necropsy there were no gross changes in the skin. The acute dermal LD_{50} in male and female rats was reported to be >3,170 mg/kg.

- Ametryn (2,000 mg/kg) was applied daily to the skin of five male and five female rats weighing approximately 200 g (Consultox Laboratories Limited, 1974). After 14 days of treatment, no deaths had occurred and no other effects were reported. The 14-day dermal LD_{50} was reported to be >2,000 mg/kg/day.

Long-term Exposure

- Domenjoz (1961) administered ametryn in water via stomach tube 6 days/week for 90 days to Meyer-Arendt rats (12/sex/dose). The initial material was 50% ametryn in a powder vehicle. Two dose levels of the material (20 or 200 mg/kg/day) provided dose levels of ametryn of 10 or 100 mg/kg/day. Two control groups were included; one group received water only and the other received the powder vehicle only suspended in water. Over the 90-day period, all animals gained weight at comparable rates and there was no visible effect on appearance or behavior. One control rat and one rat in the 100-mg/kg dosage group died. This death was not considered compound-related. At the 90-day necropsy, organ-to-body weight ratios were comparable to controls. Liver, kidney, spleen, heart, gonads, small intestine, colon, stomach, thyroid and lung were microscopically examined. The Lowest-Observed-Adverse-Effect Level (LOAEL) was associated with fatty degeneration of the liver. Based on this study, a LOAEL of 100 mg/kg/day (the highest dose tested) was identified. All tissues were comparable to controls at the lowest dose (10 mg/kg/day), which was identified as the NOAEL.

Reproductive Effects

- No information was found in the available literature on the reproductive effects of ametryn.

Developmental Effects

- No information was found in the available literature on the developmental effects of ametryn.

Mutagenicity

- Anderson et al. (1972) reported that ametryn was not mutagenic in eight strains of Salmonella typhimurium. No metabolic activating system was utilized.

- Simmons and Poole (1977) also reported that ametryn was not mutagenic in five strains of Salmonella typhimurium (TA 98, 100, 1535, 1537 and 1538), with or without metabolic activation provided by an S9 fraction from rats pretreated with Aroclor 1254.

- Shirasu et al. (1976) reported ametryn was not mutagenic in the rec-assay system utilizing two strains of Bacillus subtilis, in reversion assays utilizing auxotrophic strains of Escherichia coli (WP2) and in S. typhimurium strains TA 1535, 1536, 1537 and 1538 (without metabolic activation).

Carcinogenicity

- No information was found in the available literature on the carcinogenic effects of ametryn.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL\ or\ LOAEL) \times (BW)}{(UF) \times (\_\_\_\ L/day)} = \_\_\_\ mg/L\ (\_\_\_\ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were found in the available literature that were suitable for determination a One-day HA value for ametryn. It is, therefore, recommended that the Ten-day HA value for the 10-kg child (8.6 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Stenger and Planta (1961b) has been selected to serve as the basis for determination of the Ten-day HA value for the 10-kg child. This study identified a NOAEL of 100 mg/kg/day, based on normal weight gain and absence of histological evidence of injury in rats following 28 days of exposure by gavage. The study also identified a LOAEL of 250 mg/kg/day, based on reduced body weight gain, although no major histological changes were noted. One death occurred in the 250-mg/kg/day group, but it could not be determined if this was compound-related. The NOAEL identified in this study (100 mg/kg/day) is supported by the 28-day feeding study in rats by Piccirillo (1977), which identifed a NOAEL of 150 mg/kg/day and a LOAEL of 450 mg/kg/day, and by the study of Ceglowski et al. (1979), which identified a NOAEL of 88 mg/kg/day and a LOAEL of 880 mg/kg/day.

Using the NOAEL of 100 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(100 \text{ mg/kg/day})\ (10 \text{ kg})\ (6/7)}{(100)\ (1 \text{ L/day})} = 8.6 \text{ mg/L } (9{,}000 \text{ ug/L})$$

where:

100 mg/kg/day = NOAEL, based on absence of effects on weight gain or histology in rats dosed by gavage for 28 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from a study in animals.

6/7 = conversion from 6 to 7 days.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The 90-day oral dosing study in rats by Domenjoz (1961) has been selected to serve as the basis for determination of the Longer-term HA. At two dose levels (10 or 100 mg/kg/day), no deaths were reported and no other effects were noted during the 90-day period. Terminal necropsy findings and histological examination of tissues from treated animals were comparable to controls. At the highest dose tested, there was fatty degeneration in the livers examined. Based on these data, a NOAEL of 10 mg/kg/day (the lowest dose tested) was identified.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(10\ \text{mg/kg/day})\ (10\ \text{kg})\ (6/7)}{(100)\ (1\ \text{L/day})} = 0.86\ \text{mg/L}\ (900\ \text{ug/L})$$

where:

10 mg/kg/day = NOAEL, based on the absence of histological evidence of toxicity in rats exposed to ametryn via gavage for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from a study in animals.

6/7 = conversion from 6 to 7 days of exposure.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(10\ \text{mg/kg/day})\ (70\ \text{kg})\ (6/7)}{(100)\ (2\ \text{L/day})} = 3\ \text{mg/L}\ (3{,}000\ \text{ug/L})$$

where:

10 mg/kg/day = NOAEL, based on the absence of histological evidence of toxicity in rats exposed to ametryn via gavage for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from a study in animals.

6/7 = conversion from 6 to 7 days of exposure.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Compound-specific, chronic ingestion data for ametryn are not available at this time. In the absence of appropriate ingestion studies, the Lifetime HA for ametryn is derived from the subchronic study in rats reported by Domenjoz (1961). At two dose levels (10 or 100 mg/kg/day), no deaths were reported during the 90-day period. Terminal necropsy findings and histological examination of tissues from treated animals were comparable to controls at the lowest dose level of 10 mg/kg/day. This study identified a NOAEL of 10 mg/kg/day (the lowest dose tested).

Using the NOAEL of 10 mg/kg/day, the Lifetime HA for ametryn is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(10 \text{ mg/kg/day})\ (6/7)}{(1{,}000)} = 0.009 \text{ mg/kg/d)}$$

where:

10 mg/kg/day = NOAEL, based on absence of histological evidence of toxicity in rats exposed to ametryn via gavage for 90 days.

6/7 = conversion from 6 to 7 days exposure.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.0086 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.3 \text{ mg/L } (300 \text{ ug/L})$$

where:

0.0086 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.3 mg/L) (20%) = 0.06 mg/L (60 ug/L)

where:

0.3 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No carcinogenicity studies were found in the literature searched.
- The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenic potential of ametryn.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), ametryn may be classifed in Group D: not classified. This category is for agents with inadequate or no animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA has established residue tolerences for ametryn in or on raw agricultural commodities that range from 0.1 to 0.5 ppm (CFR, 1985).

VII. ANALYTICAL METHODS

- Analysis of ametryn is by a gas chromatographic (GC) method (#507) applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples. In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. This method has been validated in a single laboratory, and estimated detection limits have been determined for the analytes in this method, including ametryn, the estimated detection limit is 2.0 ug/L (U.S. EPA, 1988).

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) adsorption will remove ametryn from water.

- Whittaker (1980) experimentally determined adsorption isotherms for ametryn on GAC.

- Whittaker (1980) reported the results of GAC columns operating under bench-scale conditions. At a flow rate of 0.8 gpm/ft^2 and an empty bed contact time of 6 minutes, ametryn breakthrough (when effluent concentration equals 10% of influent concentration) occurred after 896 bed volumes (BV). When a bi-solute ametryn-propham solution was passed over the same column, ametryn breakthrough occurred after 240 BV.

- In a laboratory study (Nye, 1984) GAC was employed as a possible means of removing ametryn from contaminated wastewater. The results show that the column exhaustion capacity was 111.2 mg ametryn adsorbed on 1 g of activated carbon.

- Treatment technologies for the removal of ametryn from water are available and have been reported to be effective. However, selection of individual or combinations of technologies to attempt ametryn removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

AMMONIUM SULFAMATE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

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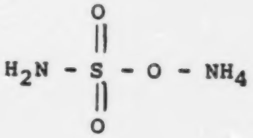
II. GENERAL INFORMATION AND PROPERTIES

CAS No. 7773-06-0

Structural Formula



$$H_2N-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-O-NH_4$$

ammonium sulfamate

Synonyms

- Amicide; Amidosulfate; Ammate; Ammonium amidosulfate; Ammonium amidosulfonate; Ammonium amidotrioxosulfate; AMS; Fyran 206k; Ikurin.

Uses

- Herbicide used to control woody plant species.
  May be used for poison ivy control in apple and pear orchards (Meister, 1986).

Properties (Meister, 1986)

Chemical Formula	$H_6N_2O_3S$
Molecular Weight	114.14
Physical State (25°C)	Colorless crystals
Boiling Point	--
Melting Point	131 to 132°C
Density (20°C)	>1
Vapor Pressure*	Negligible ($<10^{-7}$ mm Hg)
Water Solubility*	684 g/L
Specific Gravity	--
Log Octanol Water/Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

(* WSSA, 1983)

Occurrence

- No information was found in the available literature on the occurrence of ammonium sulfamate.

Environmental Fate

- Konnai et al. (1974) showed that ammonium sulfamate was very mobile in soil.

III. PHARMACOKINETICS

Absorption

- No information was found in the available literature on the absorption of ammonium sulfamate.

Distribution

- No information was found in the available literature on the distribution of ammonium sulfamate.

Metabolism

- The metabolism of ammonium sulfamate in the urine of dogs was reported by Bergen and Wiley (1938); however, details of the study were not clearly defined for assessment.

Excretion

- Bergen and Wiley (1938) reported 80 to 84% excretion of sulfamic acid in the urine of two dogs following oral administration of ammonium sulfamate in capsules for 5 days.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of ammonium sulfamate in humans.

Animals

Short-term Exposure

- An oral LD_{50} of 3,900 mg/kg in the rat is reported for ammonium sulfamate (Meister, 1986).

Dermal/Ocular Effects

- Five rats received a 20% aqueous solution of ammonium sulfamate (dose level not specified) on the shaved skin of the back. They were killed after 16 treatments on the 27th day of the period (Read and Hueber, 1938). Another five rats received a 50% aqueous solution of ammonium sulfamate on the shaved skin of the back. These animals were killed after 11 treatments on the 19th day of the study. It should be noted that the animals were not prevented from licking the chemical. Investigators reported that there were no gross pathological changes of importance in any of the animals. On microscopic pathological examination of the animals, the spleen of 9 of 10 animals had numerous macrophages with brown pigment. The stomach sections of seven animals, revealed a brown, granular material in the surface capillaries of the mucosa.

- Read and Hueber (1938) orally administered 1 mL of a 50% aqueous solution of ammonium sulfamate (1.7 g/kg/day) to 10 rats on alternate days. Five rats were killed on the 27th day of the study after nine treatments, and the remaining five were killed on the 42nd day of the study after 15 treatments. Investigators reported that there were no gross pathological changes of importance in any of the animals. Microscopic pathology indicated the following: in one animal, superficial capillaries of the stomach mucosa occasionally contained yellow-brown granules; in three animals, there was slight vacuolation of the cytoplasm of liver cells about the central veins, but these changes were very mild; and in the spleen, three of the sections had moderate numbers of macrophages filled with hemosiderin. A fourth spleen section showed marked erythrophagia.

Long-term Exposure

- Gupta et al. (1979) reported the results of a 90 days study involving oral administration of 0, 100, 250 or 500 mg/kg of ammonium sulfamate to rats (20 animals to each dose group) 6 days a week. No adverse effects were observed with respect to appearance, behavior or survival of animals. No significant difference in the body weights of rats was observed except in the case of rats receiving 500 mg/kg, where body weight was significantly less than controls after the end of 60 days. No significant changes in relative organ weights were noticed in any group of rats. Hematological examination conducted at 30, 60 and 90 days revealed nonsignificant increases in the numbers of neutrophils in the female adult and male weanling rats (500 mg/kg dose level) after 90 days. In the histological examination, organs in all the groups of animals appeared normal except that the liver of one adult rat (500 mg/kg) showed slight fatty degenerative changes after 90 days.

- Rosen et al. (1965) reported the findings of a study in female rats following administration of ammonium sulfamate at dietary levels of 1.1% (10 g/kg/day) or 2.1% (20 g/kg/day) for 105 days. No effect was detected at the 1% (10 g/kg/day) level of feeding, but growth retardation and a slight cathartic effect were observed at the 2% (20 g/kg/day) dietary level. No other information was provided by the authors.

- Sherman and Stula (1966) reported the results of a 19-month feeding study in 29-day-old CHR-CD male and female rats. Ammonium sulfamate was fed at dietary concentrations of 0, 350 or 500 ppm without any clinical or nutritional evidence of toxicity. There were no histopathological changes that could be attributed to the feeding of the test chemical. The observed pathologic lesions were interpreted as a result of spontaneous diseases.

Reproductive Effects

- Sherman and Stula (1966) reported the results of a three-generation reproduction study in rats. Rats receiving 0, 350 or 500 ppm ammonium sulfamate in the diet showed no evidence of toxicity as measured by histopathological evaluation and reproduction and lactation indices.

Developmental Effects

- No information was found in the available literature on the developmental effects of ammonium sulfamate.

Mutagenicity

- No information was found in the available literature on the mutagenic effects of ammonium sulfamate.

Carcinogenicity

- No information was found in the available literature on the carcinogenic effects of ammonium sulfamate.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were located in the available literature that were suitable for deriving a One-day HA value for ammonium sulfamate. It is recommended that the Longer-term HA value for the 10-kg child (20 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

No data on ammonium sulfamate toxicity were located in the available literature that were suitable for calculation of a Ten-day HA value. It is recommended that the Longer-term HA value for the 10-kg child (20 mg/L, calculated below) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The subchronic oral toxicity study in rats by Gupta et al. (1979) may be considered for the Longer-term HA. In this study, rats (female adults and male and female weanlings) received ammonium sulfamate orally at dose levels of 0, 100, 250 or 500 mg/kg/day for 90 days. Hematological and histological examinations at 30, 60 and 90 days revealed nonsignificant changes in hematological and histological measures. However, adult rats fed 500 mg/kg ammonium sulfamate showed lesser weight gain compared to other groups.

Using 250 mg/kg/day as a No-Observed-Adverse-Effect-Level (NOAEL), a Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(250 \text{ mg/kg/day})\ (10 \text{ kg})\ (6/7)}{(100)\ (1 \text{ L/day})} = 21.4 \text{ mg/L } (20{,}000 \text{ ug/L})$$

where:

250 mg/kg/day = NOAEL, based on the absence of hematological and histopathological changes in rats.

10 kg = assumed body weight of a child.

6/7 = conversion from 6 days to 7 days.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

For the 70-kg adult:

$$\text{Longer-term HA} = \frac{(250 \text{ mg/kg/day})\ (70 \text{ kg})\ (6/7)}{(100)\ (2 \text{ L/day})} = 75 \text{ mg/L } (80{,}000 \text{ ug/L})$$

where:

250 mg/kg/day = NOAEL, based on the absence of hematological and histopathological changes in rats.

70 kg = assumed body weight of an adult.

6/7 = conversion from 6 days to 7 days.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Gupta et al. (1979) has been selected to serve as the basis for determination of the Lifetime HA even though the results of this subchronic study were based on 90 days' exposure. In this study, rats (female adults and weanling males and females) received ammonium sulfamate orally in drinking water at dose levels of 0, 100, 250 or 500 mg/kg/day for 90 days. The NOAEL was identified as 250 mg/kg/day, since the highest dose level of 500 mg/kg/day was associated with decreased body weight gain in rats over a 90-day exposure period). In a chronic feeding study reported by Sherman and Stula (1966) in rats, ammonium sulfamate was fed to rats at dietary levels of 0, 350 or 500 ppm over a 19-month period. The authors stated that these dose levels did not produce any significant clinical or histological changes in rats receiving the test compound, and any changes recorded were interpreted as being lesions of spontaneous diseases.

Using a NOAEL of 250 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(250 \text{ mg/kg/day})\ (6/7)}{(1{,}000)} = 0.214 \text{ mg/kg/day}$$

where:

250 mg/kg/day = NOAEL.

6/7 = conversion from 6 days to 7 days.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-a-lifetime exposure.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.214 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 7.5 \text{ mg/L } (8{,}000 \text{ ug/L})$$

where:

0.214 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (7.5 mg/L) (20%) = 1.5 mg/L (2,000 ug/L)

where:

7.5 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No studies were found in the available literature investigating the carcinogenic potential of ammonium sulfamate. Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), ammonium sulfamate may be classified in Group D: not classified. This category is used for substances with inadequate or no animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The American Conference of Government Industrial Hygienists (ACGIH) has adopted a Threshold Limit Value-Time-Weighted Average (TLV-TWA) of 10 mg/m^3 and a TLV short-term exposure limit (STEL) of 20 mg/m^3 for inhalation exposure (ACGIH, 1984).

VII. ANALYTICAL METHODS

- There is no standardized method for determination of ammonium sulfamate in water samples. A procedure has been reported for the estimation of ammonium sulfamate in certain foods, however (U.S. FDA, 1969). This procedure involves a colorimetric determination of ammonium sulfamate based on the liberation of SO_4 and reduction it to H_2S, which is measured after treating with zinc, p-aminodimethylaniline and ferric chloride to form methylene blue.

VIII. TREATMENT TECHNOLOGIES

- No information was found in the available literature on treatment technologies capable of effectively removing ammonium sulfamate from contaminated water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

ATRAZINE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

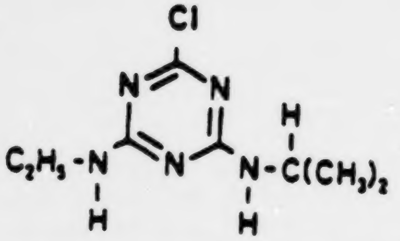
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1912-24-9

Structural Formula



2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine

Synonyms

- AAtrex; Atranex; Crisatrina; Crisazine; Farmco Atrazine; Griffex; Shell Atrazine Herbicide; Vectal SC; Gesaprim; Primatol (Meister, 1987).

Uses

- Atrazine over the past 30 years has been the most heavily used herbicide in the U.S. It is used for nonselective weed control on industrial or noncropped land and selective weed control in corn, sorghum, sugar cane, pineapple and certain other plants (Meister, 1987).

Properties (Meister, 1987; Windholz, 1976)

Chemical Formula	$C_8H_{14}ClN_5$
Molecular Weight	215.72
Physical State	White, ordorless, crystalline solid
Boiling Point (25 mm Hg)	--
Melting Point	175 to 177°C
Density (20°)	1.187
Vapor Pressure (20°C)	3.0×10^{-7} mm Hg
Water Solubility (22°C)	70 mg/L
Log Octanol/Water Partition Coefficient	2.33 to 2.71
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- In a monitoring study of Mississippi River water, atrazine residues were found at a maximum level of 17 ppb; residues were detected throughout the year, with the highest concentrations found in June or July (Newby and Tweedy, 1976).

- Atrazine has been found in 4,123 of 10,942 surface water samples analyzed and in 343 of 3,208 ground water samples (STORET, 1988).

Samples were collected at 1,659 surface water locations and 2,510 ground water locations. The 85th percentile of all non-zero samples was 2.3 ug/L in surface water and 1.9 ug/L in ground water sources. The maximum concentration found in surface water was 2,300 ug/L and in ground water it was 700 ug/L. Atrazine was foound in surface water of 31 States and in ground water in 13 States. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Atrazine has been found also in ground water in Pennsylvania, Iowa, Nebraska, Wisconsin and Maryland; typical positives were 0.3 to 3 ppb (Cohen et al., 1986).

Environmental Fate

- An aerobic soil metabolism study in Lakeland sandy loam, Hagerstown silty clay loam, and Wehadkee silt loam soils showed conversion of atrazine to hydroxyatrazine, after 8 weeks, to be 38, 40 and 47% of the amount applied, respectively, (Harris, 1967). Two additional degradates, deisopropylated atrazine and deethylated atrazine, were identified in a sandy loam study (Beynon et al., 1972).
- Hurle and Kibler (1976) studied the effect of water-holding capacity on the rate of degradation and found a half-life for atrazine of more than 125 days, 37 days and 36 days in sandy soil held at 4%, 35% and 70% water-holding capacity, respectively.
- In Oakley sandy loam and Nicollet clay loam, atrazine had a half-life of 101 and 167 days (Warnock and Leary, 1978).
- Carbon dioxide production was generally slow in several anaerobic soils: sandy loam, clay loam, loamy sand and silt loam (Wolf and Martin, 1975; Goswami and Green, 1971; Lavy et al., 1973).
- ^{14}C-Atrazine was stable in aerobic ground water samples incubated for 15 months at 10 or 25°C in the dark (Weidner, 1974).
- Atrazine is moderately to highly mobile in soils ranging in texture from clay to gravelly sand as determined by soil thin layer chromatography (TLC), column leaching, and adsorption/desorption batch equilibrium studies. Atrazine on soil TLC plates was intermediately mobile in loam, sandy clay loam, clay loam, silt loam, silty clay loam, and silty clay soils, and was mobile in sandy loam soils. Hydroxyatrazine showed a low mobility in sandy loam and silty clay loam soils (Helling, 1971).

- Soil adsorption coefficients for atrazine in a variety of soils were: sandy loam (0.6), gravelly sand (1.8), silty clay (5.6), clay loam (7.9), sandy loam (8.7), silty clay loam (11.6), and peat (more than 21) (Weidner, 1974; Lavy 1974; Talbert and Fletchall, 1965).

- Soil column studies indicated atrazine was mobile in sand, fine sandy loam, silt loan and loam; intermediately mobile in sand, silty clay loam and sandy loam; low to intermediately mobile in clay loam (Weidner, 1974; Lavy, 1974; Ivey and Andrews, 1964; Ivey and Andrews, 1965).

- In a Mississippi field study, atrazine in silt loam soil had a half-life of less than 30 days (Portnoy, 1978). In a loam to silt loam soil in Minnesota, atrazine phytotoxic residues persisted for more than 1 year and were detected in the maximum-depth samples (30 to 42 inches) (Darwent and Behrens, 1968). In Nebraska, phytotoxic residues persisted in silty clay loam and loam soils 16 months after application of atrazine; they were found at depths of 12 to 24 inches. But atrazine phytotoxic residues had a half-life of about 20 days in Alabama fine sandy loam soil, although leaching may partially account for this value (Buchanan and Hiltbold, 1973).

- Under aquatic field conditions, dissipation of atrazine was due to leaching and to dilution by irrigation water, with residues persisting for 3 years in soil on the sides and bottoms of irrigation ditches, to the maximum depth sampled, 67.5 to 90 cm (Smith et al., 1975).

- Ciba-Geigy (1988) recently submitted comments on the atrazine Health Advisory. These comments included a summary of the results of its studies on the environmental fate of atrazine. This summary indicated that laboratory degradation studies showed that atrazine is relatively stable in the aquatic medium under environmental pH conditions and indicated that atrazine degraded in soil by photolysis and microbial processes. The products of degradation are dealkylated metabolites, hydroxyatrazine and nonextractable (bound) residues. Atrazine and the dealkylated metabolites are relatively mobile whereas hydroxyatrazine is immobile.

- Ciba-Geigy (1988) also indicated that field dissipation studies conducted in California, Minnesota and Tennessee show no leaching of atrazine and metabolites below 6 to 12 inches of soil. The half-lives of atrazine in soil ranged between 20 to 101 days, except in Minnesota where degradation was slow. A forestry degradation study conducted in Oregon showed no adverse effects on either terrestial or aquatic environments. Also, Bioconcentration studies have shown low potential for bioaccummulation with a range of 15 to 77X.

III. PHARMACOKINETICS

Absorption

- Atrazine appears to be readily absorbed from the gastrointestinal tract of animals. Bakke et al. (1972) administered single 0.53-mg doses of ^{14}C-ring-labeled atrazine to rats by gavage. Total fecal excretion after 72 hours was 20.3% of the administered dose; the remainder was excreted in urine (65.5%) or retained in tissues (15.8%). This indicates that at least 80% of the dose was absorbed.

Distribution

- Bakke et al. (1972) administered single 0.53-mg doses of ^{14}C-ring-labeled atrazine to rats by gavage. Liver, kidney and lung contained the largest amounts of radioactivity, while fat and muscle had lower residues than the other tissues examined.

- In a metabolism study by Ciba-Geigy (1983a), the radioactivity of ^{14}C-atrazine dermally applied to Harlan Sprague-Dawley rats at 0.25 mg/kg was distributed to a minor extent to body tissues. The highest levels were measured in liver and muscle at all time points examined; 2.1% of the applied dose was in muscle and 0.5% in liver at 8 hours.

- Khan and Foster (1976) observed that in chickens the hydroxy metabolites of atrazine accumulate in the liver, kidney, heart and lung. Residues of both 2-chloro and 2-hydroxy moieties were found in chicken gizzard, intestine, leg muscle, breast muscle and abdominal fat.

Metabolism

- The principal reactions involved in the metabolism of atrazine are dealkylation at the C-4 and C-6 positions of the molecule. There is also some evidence of dechlorination at the C-2 position. These data were reported by several researchers as demonstrated below.

- Bakke et al. (1972) administered single 0.53-mg doses of ^{14}C-ring-labeled atrazine to rats by gavage. Less than 0.1% of the label appeared in carbon dioxide in expired air. Most of the radioactivity was recovered in the urine (65.5% in 72 hours), including at least 19 radioactive compounds. More than 80% of the urinary radioactivity was identified as 2-hydroxyatrazine and its two mono-N-dealkylated metabolites. None of the metabolites identified contained the 2-chloro moiety (which may have been removed via hydrolysis during the isolation technique or by a dechlorinating enzyme as suggested by the in vitro studies of Foster et al. (1979), who found evidence for a dechlorinase in chicken liver homogenates incubated with atrazine).

- Bohme and Bar (1967) identified five urinary metabolites of atrazine in rats: the two monodealkylated metabolites of atrazine, their carboxy acid derivatives and the fully dealkylated derivative. All of these metabolites contained the 2-chloro group. The in vitro studies of Dauterman and Muecke (1974) also found no evidence for dechlorination of atrazine in the presence of rat liver homogenates.

- Similarly, Bradway and Moseman (1982) administered atrazine (50, 5, 0.5 or 0.005 mg/day) for 3 days to male Charles River rats and observed that the fully dealkylated derivative (2-chloro-4,6-diamino-s-triazine) was the major urinary metabolite, with lesser amounts of the two mono-N-dealkylated derivatives.

- Erickson et al. (1979) dosed Pittman-Moore miniature pigs by gavage with 0.1 g of atrazine (80W). The major compounds identified in the urine were the parent compound (atrazine) and deethylated atrazine (which contains the 2-chloro substituent).

- Hauswirth (1988) indicated that the rat metabolism studies taken together are sufficient to show that in the female rat dechlorination of the triazine ring and N-dealkylation are the major metabolic pathways. Oxidation of the alkyl substituents appears to be a minor and secondary metabolic route. The total body half-life is approximately one and one-half days. Atrazine and/or its metabolites appear to bind to red blood cells. Other tissue accumulation does not appear to occur.

Excretion

- Urine appears to be the principal route of atrazine excretion in animals. Following the administration of 0.5 mg doses of ^{14}C-ring-labeled atrazine by gavage to rats, Bakke et al. (1972) reported that in 72 hours most of the radioactivity (65.5%) was excreted in the urine, 20.3% was excreted in the feces, and less than 0.1% appeared as carbon dioxide in expired air. About 85 to 95% of the urinary radioactivity appeared within the first 24 hours after dosing, indicating rapid clearance.

- Dauterman and Muecke (1974) have reported that atrazine metabolites are conjugated with glutathione to yield a mercapturic acid in the urine. The studies of Foster et al. (1979) in chicken liver homogenates also indicate that atrazine metabolism involves glutathione.

- Ciba-Geigy (1983b) studied the excretion rate of ^{14}C-atrazine from Harlan Sprague-Dawley rats dermally dosed with atrazine dissolved in tetrahydrofuran at levels of 0.025, 0.25, 2.5 or 5 mg/kg. Urine and feces were collected from all animals at 24-hour intervals for 144 hours. Results indicated that atrazine was readily absorbed, and within 48 hours most of the absorbed dose was excreted, mainly in the urine and to a lesser extent in the feces. Cumulative excretion in urine and feces appeared to be directly proportional to the administered dose, ranging from 52% at the lowest dose to 80% at the highest dose.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- A case of severe contact dermatitis was reported by Schlicher and Beat (1972) in a 40-year-old farm worker exposed to atrazine formulation. The clinical signs were red, swollen and blistered hands with hemorrhagic bullae between the fingers. Although it is noted that the exposure of this patient may have been inclusive to exposure to other chemicals in addition to atrazine, it is also noted that atrazine is a skin irritant in animal studies.

Long-term Exposure

- Yoder et al. (1973) examined chromosomes in lymphocyte cultures taken from agricultural workers exposed to herbicides including atrazine. There were more chromosomal aberrations in the workers during mid-season exposure to herbicides than during the off-season (no spraying). These aberrations included a four-fold increase in chromatid gaps and a 25-fold increase in chromatid breaks. During the off-season, the mean number of gaps and breaks was lower in this group than in controls who were in occupations unlikely to involve herbicide exposure. This observation led the authors to speculate that there is enhanced chromosomal repair during this period of time resulting in compensatory protection. However, these data may not be representative of the effect of atrazine since the exposed workers were also exposed to other herbicides.

Animals

Short-term Exposure

- Acute oral LD_{50} values of 3,000 mg/kg in rats and 1,750 mg/kg in mice have been reported for technical atrazine by Bashmurin (1974); the purity of the test compound was not specified.

- Acute oral studies conducted by Ciba-Geigy (1988) with atrazine (97% a.i.) reflected the following LD_{50}s: 1,869 mg/kg in rats and >3,000 mg/kg in mice.

- Molnar (1971) reported that when atrazine was administered by gavage to rats at 3,000 mg/kg, 6% of the rats died within 6 hours, and 25% of those remaining died within 24 hours. The rats that died during the first day exhibited pulmonary edema with extensive hemorrhagic foci, cardiac dilation and microscopic hemorrhages in the liver and spleen. Rats that died during the second day had hemorrhagic bronchopneumonia and dystrophic changes of the renal tubular mucosa. Rats sacrificed after 24 hours had cerebral edema and histochemical alterations in the lungs, liver and brain. It is noted that the dose used in this study was almost 2 x the LD_{50} (Ciba-Geigy, 1988).

- Gaines and Linder (1986) determined the oral LD_{50} for adult male and female rats to be 737 and 672 mg/kg respectively and 2,310 mg/kg for pups. It is, therefore, noted that young animals are more sensitive to atrazine than adults. This study also reflected that the dermal LD_{50} for adult rats was higher than 2,500 mg/kg.

- Palmer and Radeleff (1964) administered atrazine as a fluid dilution or in gelatin capsules to Delaine sheep and dairy cattle (one animal per dosage group). Two doses of 250 mg/kg atrazine caused death in both sheep and cattle. Sixteen doses of 100 mg/kg were lethal to the one sheep tested. At necropsy, degeneration and discoloration of the adrenal glands and congestion in lungs, liver and kidneys were observed.

- Palmer and Radeleff (1969) orally administered atrazine 80W (analysis of test material not provided) by capsule or by drench to sheep at 5, 10, 25, 50, 100, 250 or 400 mg/kg/day and to cows at 10, 25, 50, 100 or 250 mg/kg/day. The number of animals in each dosage group was not stated, and the use of controls was not indicated. Observed effects included muscular spasms, stilted gait and stance and anorexia at all dose levels in sheep and at 25 mg/kg in cattle. Necropsy revealed epicardial petechiae (small hemorrhagic spots on the lining of the heart) and congestion of the kidneys, liver and lungs. Effects appeared to be dose related. A Lowest-Observed-Adverse-Effect Level (LOAEL) of 5 mg/kg/day in sheep and a No-Observed-Adverse-Effect Level (NOAEL) of 10 mg/kg/day in cows can be identified from this study.

- Bashmurin (1974) reported that oral administration of 100 mg/kg of atrazine to cats had a hypotensive effect, and that a similar dose in dogs was antidiuretic and decreased serum cholinesterase (ChE) activity. No other details of this study were reported. Atrazine is not an organophosphate (OP), therefore, its effect on ChE may not be similar to the mechanism of ChE inhibition by OPs.

Dermal/Ocular Effects

- In a primary dermal irritation test in rats, atrazine at 2,800 mg/kg produced erythema but no systemic effects (Gzheyotskiy et al., 1977).

- Ciba-Geigy (1988) indicated that the studies it performed reflected dermal sensitization in rats but not irritation in rabbits' eyes.

Long-term Exposure

- Hazelton Laboratories (1961) fed atrazine to male and female rats for 2 years at dietary levels of 0, 1, 10 or 100 ppm. Based on the dietary assumptions of Lehman (1959), these levels correspond to doses of approximately 0, 0.05, 0.50 or 5.0 mg/kg/day. After 65 weeks, the 1.0-ppm dose was increased to 1,000 ppm (50 mg/kg/day) for the remainder of the study. No treatment-related pathology was found at 26 weeks, at 52 weeks, at 2 years, or in animals that died and were necropsied during the study. Results of blood and urine analyses were unremarkable. Atrazine had no effects on the general appearance or behavior of the rats. A transient roughness of the coat and piloerection were observed in some animals after 20 weeks of treatment at the 10- and 100-ppm levels but not at 52 weeks. Body weight gains, food consumption and survival were similar in all groups for 18 months, but from 18 to 24 months there was high mortality due to infections (not attributed to atrazine) in all groups, including controls, which limits the usefulness of this study in determining a NOAEL for the chronic toxicity of atrazine.

- In a 2-year study by Woodard Research Corporation (1964), atrazine (80W formulation) was fed to male and female beagle dogs for 105 weeks at dietary levels of 0, 15, 150 or 1,500 ppm. Based on the dietary assumptions of Lehman (1959), these levels correspond to doses of 0, 0.35, 3.5 or 35 mg/kg/day. Survival rates, body weight gain, food intake, behavior, appearance, hematologic findings, urinalyses, organ weights and histologic changes were noted. The 15-ppm dosage (0.35 mg/kg/day) produced no toxicity, but the 150-ppm dosage (3.5 mg/kg/day) caused a decrease in food intake as well as increased heart and liver weight in females. In the group receiving 1,500 ppm (35 mg/kg/day) atrazine, there were decreases in food intake and body weight gain, an increase in adrenal weight, a decrease in hematocrit and occasional tremors or stiffness in the rear limbs. There were no differences among the different groups in the histology of the organs studied. Based on these results, a NOAEL of 0.35 mg/kg/day can be identified for atrazine.

- In a study by Ciba-Geigy (1987b) using technical atrazine (97% ai.), six-month-old beagle dogs were assigned randomly to four dosage groups: 0, 15, 150 and 1,000 ppm. These doses correspond to actual average intake of 0, 0.48, 4.97 and 33.65/33.8 (male/female) mg/kg/day. Six animals/sex/group were assigned to the control and high dose groups and four animals/sex/group were assigned to the low- and mid-dose groups. One mid-dose male, one high-dose male and one high-dose female had to be sacrificed moribund during the study period. Decreased body weight gains and food consumption were noted at the high-dose level. Statistically significant ($p < 0.05$) reductions in erythroid parameters (red cell count, hemoglobin and hematocrit) in high-dose males were noted throughout the study as well as mild increases in platelet counts in both sexes. Slight decreases in total protein and albumin ($p < 0.05$) were noted in high-dose males as well as decreased calcium and chloride in males and increased sodium and glucose in females. Decrease in absolute heart weight were noted in females and increased relative liver weight in males of the high-dose group. The mid-dose females reflected an increase in the absolute heart weight and heart/brain weight ratios. The most significant effect of atrazine in this study was reflected in the high-dose animals of both sexes as discrete mycardial degeneration. Clinical signs associated with cardiac pathology such as ascites, cachexia, labored/shallow breathing and abnormal EKG were observed in the group as early as 17 weeks into the study. Gross pathology reflected severe dilation of the right atrium and occasionally of the left atrium. These findings were also noted histopathologically as degenerative atrial myocardium (atrophy and myolysis). In the mid-dose group, two males and one female appeared to be affected with the cardiac syndrome but to a much lesser degree in the intensity of the noted responses. Therefore, the LOAEL in this study is 4.97 mg/kg/day and the NOAEL is 0.48 mg/kg/day.

- A two year chronic feeding/oncogenicity study (Ciba-Geigy, 1986) was recently evaluated by the Agency. In this study, technical atrazine (98.9% a.i.) was fed to 37 to 38 days-old Sprague-Dawley rats. The dosage levels used were 0, 10, 70, 500 or 1,000 ppm, equivalent to 0, 0.5, 3.5, 25 or 50 mg/kg/day (using Lehman's conversion factor, 1959). Twenty rats per sex per group were used to measure blood parameters and clinical chemistries and urinalysis. Fifty rats per sex per goup were maintained on the treated and control diets for 24 months. An additional 10 rats per sex were placed on control and high dose (1,000 ppm) diets for a twelve month interim sacrifice and another 10 per sex (control and high dose, 1,000 ppm) for a 13 month sacrifice (the 1,000 ppm group was placed on control diet for one month prior to sacrifice). The total number of animals/sex in the control and HDT groups was 90 and 70 for the 10, 70 and 500 ppm groups. Histopathology was performed on all animals. At the mid- and high-dose, there was a decrease in mean body weights of males and females. Survival was decreased in high-dose females but increased in high-dose males. There were decreases in organ-to-body weight ratios in high-dose animals, which were probably the result of body weight decreases. Hyperplastic changes in high-dose males (mammary gland, bladder and prostate) and females (myeloid tissue of bone marrow and transitional epithelium of the kidney) were of questionable toxicologic importance. There was an increase in retinal degeneration and in centrolobular necrosis of the liver in high-dose females and an increase in degeneration of the rectus femoris muscle in high-dose males and females when compared to controls. Based on decreased body weight gain, the LOAEL for non-oncogenic activities in both sexes is 25 mg/kg/day and the NOAEL is 3.5 mg/kg/day. However, oncogenic activities were noted at 3.5 mg/kg/day (70 ppm) and above as reflected in the increased incidence of mammary gland tumors in females.

° A recent 91-week oral feeding/oncogenicity study in mice by Ciba-Geigy (1987c) has been evaluated by the Agency. In this study, atrazine (97% ai.) was fed to five-weeks-old CD-1 strain of mice, weighing 21.0/26.8 grams (female/male). The mice were randomly assigned to five experimental groups of approximately 60 animals/sex/group. The dosage tested were 0, 10, 300, 1,500 and 3,000 ppm; these dosages correspond to actual mean daily intake of 1.4, 38.4, 194.0 and 385.7 mg/kg/day for males, and 1.6, 47.9, 246.9 and 482.7 mg/kg/day for females. This study shows that there are dose-related effects at 1,500 ppm or 3,000 ppm atrazine: an increase in cardiac thrombi, a decrease in the mean body weight gain at 12 and 91 weeks during the study, and decreases in erythrocyte count, hematocrit and hemoglobin concentration. Cardiac thrombi contributed to the deaths of the group of mice that did not survive to terminal sacrifice. The LOAEL is set at 1,500 ppm based upon decreases of 23.5% and 11.0% in mean body weight gain found at 91 weeks in male and female mice, respectively. Also, an increase in the incidence of cardiac thrombi is found in female mice in the 1,500 ppm exposure group. None of the above effects are found at 300 ppm, thus the NOAEL is set at 300 ppm (corresponding to 38.4 mg/kg/day in males and 47.9 mg/kg/day for females).

Reproductive Effects

° A three-generation study on the effects of atrazine on reproduction in rats was conducted by Woodard Research Corporation (1966). Groups of 10 males and 20 females received atrazine (80W) at dietary levels of 0, 50 or 100 ppm. Based on the dietary assumptions that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of approximately 0, 2.5 or 5 mg/kg/day. Two litters were produced per generation but parental animals were chosen from the second litter after weaning for each generation. Young rats were maintained on the test diets for approximately ten weeks in each generation. The third generation pups were sacrificed after weaning. It is noted that the parental animals of the first generation were fed only half of the dietary atrazine levels for the first 3 weeks of exposure. There were no adverse effects of atrazine on reproduction observed during the course of the three-generation study. A NOAEL of 100 ppm (5 mg/kg/day) was identified for this study. However, the usefulness of this study is limited due to the alteration of the atrazine content of the diet during important maturation periods of the neonates.

- A recent two-generations study in rats by Ciba-Geigy (1987a) was conducted using the 97% ai. technical atrazine. Young rats, 47 to 48 days old were maintained on the control and test diets for 10 weeks before mating. The concentrations used were 0, 10, 50 and 500 ppm (equivalent to 0, 0.5, 2.5 and 25 mg/kg/day using Lehman conversion factor, 1959). Thirty animals/sex/group were used in each generation; one litter was produced per generation. The level tested had no effect on mortality in either generation. Body weight and body weight gains were significantly depressed ($p < 0.05$) at the highest dose; however, food consumption was also decreased at this high-dose level in parental males and females during the premating period and for the first generation females (F_1) on days 0 to 7 of gestation. No histopathological effects were noted nor other effects were noted during gross necropsy in either parental generation with the exception of increased testes relative weight in both generations at the high dose. In pups of both generation, significant reduction ($p < 0.05$) in body weight was noted; however, this effect was only dose-related in the second generation (F_2) at both the mid- and high-dose levels on postnatal day 21. Therefore, maternal toxicity NOAEL is 2.5 mg/kg/day; the reproductive LOAEL is 2.5 mg/kg/day (reduced pup weight in F_2 generation on postnatal day 21) and the NOAEL is 0.5 mg/kg/day.

Developmental Effects

- In the three-generation reproduction study in rats conducted by Woodard Research Corporation (1966) (described above), atrazine at dietary levels of 50 or 100 ppm (2.5 or 5 mg/kg/day) resulted in no observed histologic changes in the weanlings and no effects on fetal resorption. No malformations were observed, and weanling organ weights were similar in controls and atrazine-treated animals. Therefore, a NOAEL of 100 ppm (5 mg/kg/day) was also identified for developmental effects in this study. However, the usefulness of this study is limited due to an alteration of the atrazine content of the diet during important maturation periods of the neonates.

- Atrazine was administered orally to pregnant rats on gestation days 6 to 15 at 0, 100, 500 or 1,000 mg/kg (Ciba-Geigy, 1971). The two higher doses increased the number of embryonic and fetal deaths, decreased the mean weights of the fetuses and retarded the skeletal development. No teratogenic effects were observed. The highest dose (1,000 mg/kg) resulted in 23% maternal mortality and various toxic symptoms. The 100 mg/kg dose had no effect on either dams or embryos and is therefore the maternal and fetotoxic NOAEL in this study.

- In a study by Ciba-Geigy (1984a), Charles River rats received atrazine (97%) by gavage on gestation days 6 to 15 at dose levels or 0, 10, 70, or 700 mg/kg/day. Excessive maternal mortality (21/27) was noted at 700 mg/kg/day, but no mortality was noted at the lower doses; also reduced weight gains and food consumption were noted at both 70 and 700 mg/kg/day. Developmental toxicity was also present at these dose levels. Fetal weights were severely reduced at 700 mg/kg/day; delays in skeletal development occurred at 70 mg/kg/ day, and a dose-related runting was noted at 10 mg/kg/day and above. The NOAEL for maternal toxicity appears to be 10 mg/kg/day, however, this is also the LOAEL for developmental effects.

- New Zealand white rabbits received atrazine (96%) by gavage on gestation days 7 through 19 at dose levels of 0, 1, 5 or 75 mg/kg/day (Ciba-Geigy, (1984b). Maternal toxicity, evidenced by decreased body weight gains and food consumption, was present in the mid- and high-dose groups. Developmental toxicity was demonstrated only at 75 mg/kg/day by an increased resorption rate, reduced fetal weights, and delays in ossification. No teratogenic effects were indicated. The NOAEL appears to be 1 mg/kg/day.

- Peters and Cook (1973) fed atrazine to pregnant rats (four/group) at levels of 0, 50, 100, 200, 300, 400, 500 or 1,000 ppm in the diet throughout gestation. Based on an assumed body weight of 300 g and a daily food consumption of 12 g (Arrington, 1972), these levels correspond to approximately 0, 2, 4, 8, 12, 16, 20 or 40 mg/kg/day. The number of pups per litter was similar in all groups, and there were no differences in weanling weights. This study identified a NOAEL of 40 mg/kg/day for developmental effects. In another phase of this study, the authors demonstrated that subcutaneous (sc) injections of 50, 100 or 200 mg/kg atrazine on gestation days 3, 6 and 9 had no effect on the litter size, while doses of ≥800 mg/kg were embryotoxic. Therefore, a NOAEL of 200 mg/kg by the sc route was identified for embryotoxicity.

Mutagenicity

- Loprieno et al. (1980) reported that single doses of atrazine (1,000 mg/kg or 2,000 mg/kg, route not specified) produced bone marrow chromosomal aberrations in the mouse. No other details of this study were provided.

- Murnik and Nash (1977) reported that feeding 0.01% atrazine to male *Drosophila melanogaster* larvae significantly increased the rate of both dominant and sex-linked recessive lethal mutations. They stated, however, that dominant lethal induction and genetic damage may not be directly related.

- Adler (1980) reviewed unpublished work on atrazine mutagenicity carried out by the Environmental Research Programme of the Commission of the European Communities. Mutagenic activity was not induced even when mammalian liver enzymes (S-9) were used; however, the use of plant microsomes produced positive results. Also, in *in vivo* studies in mice, atrazine induced dominant lethal mutations and increased the frequency of chromatid breaks in bone marrow. Hence, the author suggested that activation of atrazine in mammals occurs independently of the liver, possibly in the acidic part of the stomach.

- As described previously, Yoder et al. (1973) studied chromosomal aberrations in the lymphocyte cultures of farm workers exposed to various pesticides including atrazine. During mid-season a 4-fold increase in chromatid gaps and a 25-fold increase in chromatid breaks was observed. During the off-season (no spraying), the number of gaps and breaks was lower than in controls, suggesting to the authors that there is enhanced chromosomal repair during the unexposed period.

- Recently, Spencer (1987) and Dearfield (1988) evaluated several in vitro and in vivo mutagenicity studies on atrazine that were recently submitted to the U.S. EPA by Ciba-Geigy. They noted that most of these studies were inadequate with the exception of the following three tests: a Salmonella assay; an E. coli reversion assay; and a Host-Mediated assay. The first two assays were negative for mutagenic effects; the results of the third assay were equivocal.

- Ciba-Geigy (1988) indicated that Brusick (1987) evaluated atrazine mutagenicity and that the weight-of-evidence analysis he used placed the chemical in a non-mutagenic status. The Agency (Dearfield, 1988) evaluated Brusick's analysis. It is noted that the use of the weight-of-evidence approach is not appropriate at the present time. The in vivo studies by Adler (1980) suggest a positive response. These findings have not been diminished by other atrazine studies. In addition, Dearfield (1988) indicated that the scheme used by Brusick in this analysis is flawed by the lack of calibration of the chemical test scores to an external standard and by the use of some studies that are considered inadequate by design to determine the mutagenic potential of atrazine.

Carcinogenicity

- Innes et al. (1969) investigated the tumorigenicity of 120 test compounds including atrazine in mice. Two F_1 hybrid stocks (C57BL/6 x Anf) F_1 and (C57BL/6 x AKR) F_1 were used. A dose of 21.5 mg/kg/day was administered by gavage to mice of both sexes from age 7 to 28 days. After weaning at 4 weeks, this dose level was maintained by feeding 82 ppm atrazine ad libitum in the diet for 18 months. The incidence of hepatomas, pulmonary tumors, lymphomas and total tumors in atrazine-treated mice was not significantly different from that in the negative controls.

- A two-year feeding/oncogenicity study in rats by Ciba-Geigy (1986) has been evaluated recently by the Agency. Atrazine (98.9% a.i.) was fed to 37 to 38 days-old Sprague-Dawley rats. The dosage levels used were 0, 10, 70, 500 or 1,000 ppm, equivalent to 0, 0.5, 3.5, 25 or 50 mg/kg/day (using Lehman's conversion factor, 1959). The total number of animals/sex in the control and HDT groups was 90; and 70 animals/sex/group for the 10, 70 and 500 ppm groups. Histopathology was performed on all animals. In females, atrazine was associated with a statistically significant increase in mammary gland fibroadenomas at 1,000 ppm, in mammary gland adenocarcinomas (including two carcinosarcomas at the HDT) at 70, 500 and 1,000 ppm, and in total mammary gland tumor bearing animals at 1,000 ppm. Each of these increases was associated with a statistically significant dose-related trend and was outside of the high end of the historical control range. In addition, U.S. EPA (1986a) indicated that there was evidence for decreased latency for mammary gland adenocarcinomas at the 12 month interim sacrifice that was already submitted by Ciba-Geigy in 1985. This study was also reported as positive in a briefing paper by Ciba-Geigy (1987).

° A recent 91-week oral feeding/oncogenicity study in mice by Ciba-Geigy (1987c) has been evaluated by the Agency. In this study, atrazine (97% ai.) was fed to five-weeks-old CD-1 mice weighing 21.0/26.8 grams (female/male). The mice were randomly assigned to five experimental groups of approximately 60 animals/sex/ group. The dosage tested were 0, 10, 300, 1,500 and 3,000 ppm; these dosages correspond to actual mean daily intake of 1.4, 38.4, 194.0 and 385.7 mg/kg/day for males, and 1.6, 47.9, 246.9 and 482.7 mg/kg/day for females. The following kinds of neoplasms were noted in this study: mammary adenocarcinomas, adrenal adenomas, pulmonary adenomas and malignant lymphomas. However, no dose-related or statistically significant increases were observed in the incidences of these neoplasms. Therefore, atrazine is not considered oncogenic in this strain of mice.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000) in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable information was found in the available literature for the determination of the One-day HA value for atrazine. It is, therefore, recommended that the Ten-day HA value calculated below for a 10-kg child of 0.1 mg/L (100 ug/L), be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

Two teratology studies by Ciba-Geigy, one in the rat (1984a) and one in the rabbit (1984b), were considered for the calculation of the Ten-day HA value. The rat study reflected a NOAEL of 10 mg/kg/day for maternal toxicity but this value was also the LOAEL for developmental toxicity while the rabbit study reflected NOAELs of 5 mg/kg/day for developmental toxicity and 1 mg/kg/day for maternal toxicity. Thus, the rabbit appears to be a more sensitive species than the rat for maternal toxicity, hence, the rabbit study with a NOAEL of 1 mg/kg/day is used in the calculations below.

The Ten-day HA for a 10 kg child is calculated below as follows:

$$\frac{(1 \text{ mg/kg/d}) \times (10\text{kg})}{(100) \times (1 \text{ L/day})} = 0.1 \text{ mgL } (100 \text{ ug/L})$$

where:

1 mg/kg/day = NOAEL, based on maternal toxicity evidenced by decreased body weight gain and food consumption.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or ODW/NAS guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily consumption for a child.

Longer-term Health Advisory

No suitable information was found in the available literature for the determination of the longer-term HA value for atrazine. It is, therefore, recommended that the adjusted DWEL for a 10-kg child of 0.05 mg/L (50 ug/L) and the DWEL for a 70-kg adult of 0.2 mg/L (200 ug/L) be used at this time as conservative estimates of the Longer-term HA values.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986b), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Three studies were considered for the development of the Lifetime HA. A two-year dog feeding study (Woodard, 1964), a one-year dog feeding study Ciba-Geigy, 1987b) and a two-year rat oral feeding/oncogenicity study (Ciba-Geigy, 1986).

The first study in dogs (1964) reflected a NOAEL of 0.35 mg/kg/day and a LOAEL of 3.5 mg/kg/day that was associated with increased heart and liver weights in females. The new one-year dog study (1988) reflected a NOAEL of 0.48 mg/kg/day and a LOAEL of 4.97 mg/kg/day based on mild cardiac pathology intensified at the higher dose tested 33.65/33.8 (male/female) mg/kg/day. The two-year rat study (Ciba-Geigy, 1986) reflected a NOAEL at 3.5 mg/kg/day for systemic effect other than oncogenicity; however, this study indicated that atrazine caused mammary gland tumors at this dose level and above, no adverse effects were observed at the lowest dose tested, 0.5 mg/kg/day.

The 1964 dog study was initially used for the calculation of the RfD and the Lifetime HA. However, this study was partially flawed by the lack of information on the purity of the test material and by the inadequate documentation of the hematological data. Therefore, the recent one-year dog study (Ciba-Geigy, 1987b), using technical atrazine (97% ai.), is considered as a more adequate study for the calculation of the RfD and the Lifetime HA. The NOAEL in this study, 0.48 mg/kg/day, is also supported by the NOAEL of 0.5 mg/kg/day in the two-generation reproduction study (Ciba-Geigy, 1987a) and by the fact that no systemic effects or tumors were noted at this dose level in the two-year chronic feeding/oncogenicity study in rats (Ciba-Geigy, 1986). [Other studies: Woodard Research Corporation (1966) and Hazelton Laboratories (1961) identified long-term NOAEL values of 5 to 50 mg/kg/day and were not considered to be as protective as the dog studies for use in calculating the HA values for atrazine.]

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{0.48 \text{ mg/kg/day}}{(100)} = 0.005 \text{ mg/kg/day}$$

(rounded from 0.0048 mg/kg/day)

where:

0.48 mg/kg/day = NOAEL, based on the absence of cardiac pathology or any other/adverse clinical, hematological, biochemical and histopathological effects in dogs.

100 = uncertainty factor, chosen in accordance with EPA or ODW/NAS guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.0048 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.168 \text{ mg/L } (200 \text{ ug/L})$$

where:

0.0048 mg/kg/day = RfD (before rounding off to 0.005 mg/kg/day)

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(0.168 \text{ mg/L})\ (20\%)}{10} = 0.003 \text{ mg/L } (3 \text{ ug/L})$$

where:

0.168 mg/L = DWEL (before rounding off to 0.2 mg/L)

20% = assumed relative source contribution from water.

10 = additional uncertainty factor, according to ODW policy, to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- A study submitted by Ciba-Geigy Corporation (1986) in support of the pesticide registration of atrazine indicated that atrazine induced an increased incidence of mammary tumors in female Sprague-Dawley rats. These findings have been further confirmed in a briefing by Ciba-Geigy (1987) on this study.
- Atrazine was not oncogenic in mice (Ciba-Geigy, 1987c).
- Three closely related analogs: propazine, terbutryn and simazine are presently classified as Group C oncogens based on an increased incidence of tumors in the same target tissue (mammary gland) and animal species (rat) as was noted for atrazine.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of atrazine.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), atrazine may be classified in Group C: possible human carcinogen. This category is used for substances with limited evidence of carcinogenicity in animals in the absence of human data.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Toxicity data on atrazine were reviewed by the National Academy of Sciences (NAS, 1977), and the study by Innes et al. (1969) was used to identify a chronic NOAEL of 21.5 mg/kg/day. Although at that time it was concluded that atrazine has low chronic toxicity, an uncertainty factor of 1,000 was employed in calculation of the ADI from that study, since only limited data were available. The resulting value (0.021 mg/kg/day) corresponds to an ADI of 0.73 mg/L in a 70-kg adult consuming 2 L of water per day.

- Tolerances for atrazine alone and the combined residues of atrazine and its metabolites in or on various raw agricultural commodities have been established (U.S. EPA, 1986c). These tolerances range from 0.02 ppm (negligible) in animal products (meat and meat by-products) to 15 ppm in various animal fodders.

VII. ANALYTICAL METHODS

- Analysis of atrazine is by a gas chromatographic (GC) method, Method No. 507, applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 L of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. The method has been validated in a single Laboratory. The estimated detection limit for the analytes in this method, including atrazine, is 0.13 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove atrazine from water include activated carbon adsorption, ion exchange, reverse osmosis, ozone oxidation and ultraviolet irradiation. Conventional treatment methods have been found to be ineffective for the removal of atrazine from drinking water (ESE, 1984; Miltner and Fronk, 1985a). Limited data suggest that aeration would not be effective in atrazine removal (ESE, 1984; Miltner and Fronk, 1985a).

- Baker (1983) reported that a 16.5-inch GAC filter cap using F-300, which was placed upon the rapid sand filters at the Fremont, Ohio water treatment plant, reduced atrazine levels by 30 to 64% in the water from the Sandusky River. At Jefferson Parish, Louisiana, Lykins et al. (1984) reported that an adsorber containing 30 inches of Westvaco WV-G® 12 x 40 GAC removed atrazine to levels below detectable limits for over 190 days.

- At the Bowling Green, Ohio water treatment plant, PAC in combination with conventional treatment achieved an average reduction of 41% of the atrazine in the water from the Maumee River (Baker, 1983). Miltner and Fronk (1985a) reported that in jar tests using spiked Ohio River water with the addition of 16.7 and 33.3 mg/L of PAC and 15-20 mg/L of alum, PAC removed 64 and 84%, respectively, of the atrazine. Higher percent removals reflected higher PAC dosages. Miltner and Fronk (1985b) monitored atrazine levels at water treatment plants, which utilized PAC, in Bowling Green and Tiffin, Ohio. Applied at dosages ranging from 3.6 to 33 mg/L, the PAC achieved 31 to 91% removal of atrazine, with higher percent removals again reflecting higher PAC dosages.

- Harris and Warren (1964) reported that Amberlite IR-120 cation exchange resin removed atrazine from aqueous solution to less than detectable levels. Turner and Adams (1968) studied the effect of varying pH on different cation and anion exchange resins. At a pH of 7.2, 45% removal of atrazine was achieved with Dowex® 2 anion exchange resin and with $H_2PO_4^-$ as the exchangeable ion species.

- Chian et al. (1975) reported that reverse osmosis, utilizing cellulose acetate membrane and a cross-linked polyethelenimine (NS-100) membrane, successfully processed 40% of the test solution, removing 84 and 98%, respectively, of the atrazine in the solution.

- Miltner and Fronk (1985a) studied the oxidation of atrazine with ozone in both spiked distilled and ground water. Varying doses of ozone achieved a 70% removal of atrazine in distilled water and 49 to 76% removal of atrazine in ground water.

- Kahn et al. (1978) studied the effect of fulvic acid upon the photochemical stability of atrazine to ultraviolet irradiation. A 50% removal of atrazine was achieved much faster at higher pH conditions than at lower pH conditions. In the presence of fulvic acids, the time needed for ultraviolet irradiation to achieve 50% removal was almost triple the time required to achieve similar removals without the presence of fulvic acids. Since fulvic acids will be present in surface waters, ultraviolet irradiation may not be a cost-effective treatment alternative.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

(BAYGON) Propoxur

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

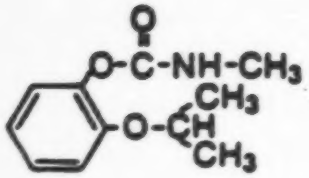
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 114-26-1

Structural Formula



2-(1-Methylethoxy)-phenol methylcarbamate

Synonyms

- Baygon Propoxur (proposed common name); Aprocarb; Blattanex; BAY 39007; Bayer 39007; Pillargon; Propyon; Suncide; Tugon; OMS 33; Unden (Meister, 1984).

Uses

- A nonfood insecticide used on humans, animals and turf grass (Meister, 1984).
- Propoxur is an insecticide currently registered for use on a variety of terrestial non-food (ornamentals, lawns, and general outdoor areas), aquatic non-food (sewage systems and stagnant water), forestry, domestic outdoor, and indoor sites. Application rates are dependent on use. For use as a bait, applications include 1.81-18.14 g/1,000 sq ft. For use on turf, applications include 39.69-85.05 g/1,000 sq ft. For outdoor uses, applications include 0.046-0.175 lb/A, 0.375-1.125 lb/mile with a 300 ft swath, 0.493-2% finished spray, 0.14-0.45/1,000 sq ft, 2.1% D applied directly to ant hills, and 6 strips containing 10% Impr/gypsy month monitoring trap. For treatment of premises, applications include 0.25-1% finished spray and 0.06-0.28 g/1,000 sq ft. For indoor treatments, applications include 0.25% G, 0.25-2% P/T, 0.25-1.7% Impr, 1% RTU in traps/bait trays, one fly strip containing 0.4% Impr/1,000 cu ft, contact strips containing 4-10% Impr, shelf paper containing 0.6-1% Impr, and 0.493-2% finished spray. For treatment of animals, applications include 0.9% Impr (dab-on), 9.4% Impr (collars), 8.5-56.7 g/gal (dips), 0.125% RTU (shampoo), and 0.25-0.28% finished spray. Propoxur may be applied with ground or aerial equipment.

Properties (ACGIH, 1984; Meister, 1984; Worthing, 1983; and CHEMLAB, 1985)

Chemical Formula	$C_{11}H_{15}O_3N$
Molecular Weight	209.24
Physical State (at 25°C)	White to tan crystalline solid
Boiling Point	--
Melting Point	91°C
Density (°C)	--
Vapor Pressure (120°C)	0.01 mmHg
Water Solubility (20°C)	2000 mg/L
Log Octanol/Water Partition Coefficient	0.14
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Baygon has been found in 85 of 624 surface water samples analyzed and in 0 of 114 ground water samples (STORET, 1988). Samples were collected at 21 surface water locations and 111 ground water locations. The 85th percentile of all mean-zero samples was 0.96 ug/L in surface water. The maximum concentration found in surface water was also 0.96 ug/L. Baygon was found only in surface water and this finding was reported only in Michigan and Ohio. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Ring-labeled ^{14}C-propoxur (radiochemical purity 97%), at 5 ppm, degrades with a half-life of >28 days in irradiated and non-irradiated dry sandy loam soil (McNamara and Moore, 1981). Propoxur comprised 75% of the applied in the irradiated soil at 28 days post-treatment. 2-(1-Methylethoxy)phenol comprised <2% in both irradiated and non-irradiated soil at all sampling intervals. Approximately 1% of the applied radioactivity was isolated in trapping solutions from the irradiated samples. Radioactivity was not detected in trapping solutions from dark control samples.

- ^{14}C-Propoxur (radiochemical purity >95%), at 0.94-98.6 ug/10 mL, was very mobile (Freundlich K_{aas} 0.05-0.30) in sandy loam, silt loam, and silty clay soil:distilled water slurries (1:5 soil:solution ratio) based on batch ecuilibrium studies (Lenz and Gronberg, 1980). Desorption was quite variable; 0-100% (0-5.9 ug/10 mL) of the adsorbed was desorbed from the soil.

- Aged (28 days) ring- and carbonyl-labeled ^{14}C-propoxur residues (78-89% propoxur) were very mobile in columns (12-inch length) of silt loam soil leached with 22.5 inches of water over a 45-day period (Atwell, 1976). Between 69 and 74% of the recovered ^{14}C-residues were leached through the columns. The remaining residues were distributed evenly throughout the columns. In the leachate, 100% of the carbonyl-labeled ^{14}C-residues and 77% of the ring-labeled ^{14}C-residues were identified as propoxur; 23% of the ring-labeled ^{14}C-residues were 2-(1-methylethoxy)phenol.

- Unaged ^{14}C-propoxur (radiochemical purity >98%), was mobile in columns of sandy loam and silt loam soil; 70-79% of the applied radioactivity was leached from the columns (Moellhoff, 1983). Propoxur was the major ^{14}C-compound in both the leachates and the columns treated with unaged propoxur. Aged (30 days) ^{14}C-propoxur residues were slightly mobile in both soils; 72-75% of the applied radioactivity remained in the soil columns. Propoxur was the predominant compound in both the soil and leachate after leaching.

  Propoxur was very mobile on sand, sandy loam, sandy clay loam, silt loam, and silty clay soil TLC plates, with R_f values ranging from 0.70 to 0.89 (Thornton et al., 1976).

III. PHARMACOKINETICS

Absorption

- Vandekar et al. (1971) administered a single oral dose of 1.5 mg/kg of propoxur, 95% active ingredient (a.i.), to a 42-year-old male volunteer. About 45% of the dose was recovered in urine within 24 hours as o-isopropoxyphenol. Since vomiting occurred 23 minutes after ingestion, the authors assumed that much of the dose was expelled by this route, so the percent actually absorbed could not be calculated.

- Chemagro Corp. (no date) investigated the dermal absorption of ^{14}C-labeled Baygon in human subjects. Baygon (4 ug/cm^2, total dose less than 1 mg) was applied to the forearm of the subjects(s) in four tests: (1) application to the skin without preparation, (2) application after stripping of the skin with an adhesive tape, (3) application followed by occlusion and (4) application followed by induction of sweating. The amounts excreted (route not specified, but presumably in urine) after these treatments were 20, 51, 64 and 18%, respectively, indicating that Baygon is absorbed through the skin.

- Krishna and Casida (1965) administered single oral doses of ^{14}C-labeled Baygon (50 mg/kg) to Sprague-Dawley rats. After 48 hours, about 4% of the dose had been excreted in feces, and the remainder was detected in urine (64 to 72%), expired air (26%) or the body (4.2 to 7.9%). This indicated that Baygon had been well absorbed (at least 96%) from the gastrointestinal tract. Similar findings were reported by Foss and Krechniak (1980).

Distribution

- Foss and Krechniak (1980) investigated the fate of Baygon after oral administration of 50 mg/kg to male albino rats. Analysis of tissues indicated that Baygon levels were greatest in the kidneys, with somewhat lower levels in the liver, blood and brain.

Metabolism

- Dawson et al. (1964) administered single oral doses of 92.2 mg of Baygon (purity not specified) to six male volunteers, and single oral doses of 50 mg to three subjects. Urine samples were collected and analyzed for metabolites. A material identified as 2-isopropoxyphenol was observed in the urine of both groups. Similar results were reported by Vandekar et al. (1971).

- Foss and Krechniak (1980) investigated the metabolism of Baygon after both oral and intravenous administration of 50 mg/kg to male albino rats. Isopropoxyphenol was detected in tissues 10 minutes following administration, and the highest concentrations were attained between 30 and 60 minutes after dosing. This metabolite prevailed in the blood and liver, but in the kidney only unchanged Baygon could be detected. Eight hours postdosing, only traces of Baygon and its metabolites were detected in these tissues.

- Everett and Gronberg (1971) studied the metabolism of Baygon in Holtzman rats. Animals were dosed by gavage with Baygon (5 to 10 mg/kg) labeled with ^{14}C or ^{3}H in the carbonyl or the isopropyl groups. Pooled urine from eight rats (four/sex) dosed with 20 mg/kg/day of unlabeled Baygon for 4 days was used to isolate sufficient quantities of metabolites for identification of structure. Results indicated that the major pathway of Baygon metabolism involved depropylation to 2-hydroxyphenol-N-methyl carbamate and hydrolysis of the carbamate to isopropoxyphenol. Minor pathways involved ring hydroxylation at the five- or six-position, secondary hydroxylation of the 2'-carbon of the isopropoxy group and N-methyl hydroxylation. Metabolites that contained the 6-hydroxy group formed N-conjugates, while those that contained the 5-hydroxy group formed O-glucuronides.

Excretion

- Dawson et al. (1964) reported that in humans given a single oral doses of 92.2 mg Baygon (purity not specified), 38% of the dose was excreted as phenols in urine over the next 24 hours; most was excreted in the first 8 to 10 hours.

- Krishna and Casida (1965) administered single oral doses of 50 mg/kg of ^{14}C-carbonyl-labeled Baygon to Sprague-Dawley rats. After 48 hours, recovery of label in excretory products was as follows: 64% (males) and 72% (females) in urine; 4% in feces (males and females); and 26% in expired carbon dioxide (males and females). Residual label in the body was 4.2% (males) and 7.9% (females). One-third of the excreted dose was hydrolyzed, with most of the remainder being intact.

- Everett and Gronberg (1971) reported that 85% of orally administered ^{14}C-carbonyl-labeled Baygon (5 to 8 mg/kg) was recovered from Holtzman rats within 16 hours of dosing; 20 to 25% of the radioactivity appeared in the expired air, and 60% of the radioactivity appeared in the urine as conjugates. Also, Foss and Krechniak (1980) indicated that 85 to 95% of an oral dose (50 mg/kg) administered to male albino rats was excreted in urine with a half-life of 0.18 to 0.26 hour.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- Vandekar et al. (1971) studied the acute oral toxicity of Baygon in human volunteers. A 42-year-old man ingested a single oral dose of 1.5 mg/kg of propoxur (Baygon) (95% a.i., recrystallized). Cholinergic symptoms, including blurred vision, nausea, sweating, tachycardia and vomiting, began about 15 to 20 minutes after exposure. Effects were transient and disappeared within 2 hours. Cholinesterase (ChE) activity (measured spectrophotometrically) in red blood cells decreased to 27% of control values by 15 minutes after exposure, and returned to control levels by 2 hours. No effect was detected in plasma ChE activity. In a second test, a single dose of 0.36 mg/kg caused short-lasting stomach discomfort, blurred vision and moderate facial redness and sweating. Red blood cell ChE activity fell to 57% of control values within 10 minutes, then returned to control levels within 3 hours.

- Vandekar et al. (1971) administered five oral doses of 0.15 or 0.20 mg/kg to male volunteers at half-hour intervals (total dose of 0.75 or 1.0 mg/kg). In each subject, a symptomless depression of red blood cell ChE was observed; the lowest level, about 60% of control values, was reached between 1 and 2 hours following doses 3, 4 and 5. After the final dose, red blood cell ChE activity rose to control levels within about 2 hours. The authors noted that a dose of Baygon was tolerated better if it was divided into portions and given over time than if it was given as a single dose.

Long-term Exposure

- Davies et al. (1967) described the effects of a large-scale spraying operation in El Salvador in which Baygon (OMS-33, 100% a.i.) was used. The trial was planned so that medical assistance would be available, and appropriate clinical support could be provided to those affected by the spraying. The total amount of OMS-33 sprayed was 345 kg. Among the spraymen, exposure (expressed in person-days) was 70.5; 19 experienced symptoms (26% incidence). In the general population, the exposure was 3,340 person-days, and 35 experienced symptoms (1% incidence). The primary symptoms were headache, vomiting and nausea. In the spraymen, the symptoms occurred mostly in the first days, with no visible symptoms after that time. In severe cases, atropine was administered as an antidote. It was concluded that the acute toxicity symptoms were observed in a low incidence, and they were, in general, mild, evanescent, reversible, responsive to small doses of atropine, and tended to occur at the beginning of the spray program.

- Montazemi (1969) reported on the toxic effects of Baygon on the population of 26 villages in Iran that were sprayed with Baygon at the rate of 2 g/m^2 daily for 18 days. Selected inhabitants from six villages and sprayers were examined on days 2, 8 and 18 and after the completion of the spraying. Depression of ChE activity was found in the inhabitants and in the sprayers, but the sprayers generally had more severe symptoms. Atropine or belladonna was adequate to treat those exhibiting symptoms.

Animals

Short-term Exposure

- The acute oral LD_{50} value for technical Baygon (purity not specified) in male and female Sherman rats was reported to be 83 and 86 mg/kg, respectively (Gaines, 1969). The oral LD_{50} was reported to be 23.5 mg/kg in mice and 40 mg/kg in guinea pigs (NIOSH, 1987).

- Farbenfabriken Bayer (1961) determined an oral LD_{50} of 100 to 150 mg/kg (purity not specified) in male albino rats. Severe muscle spasms were observed, but no dose-response information was provided.

- Eben and Kimmerle (1973) studied the acute toxicity of Baygon in SPF-Wistar rats. Single oral doses of propoxur (98.7% a.i.), diluted with propylene glycol, were given by gavage to groups of three male rats at levels of 15, 20, 40 or 60 mg/kg; female rats were given doses of 10, 20, 40 or 60 mg/kg. Cholinesterase levels were measured in plasma, erythrocytes and brain at 10, 20 and 180 minutes after dosing. Maximum ChE depression was observed at 10 and 20 minutes in the plasma and erythrocytes, and at 180 minutes in the brain. The inhibition was dose-dependent and a no-effect level was not observed. In plasma, ChE was inhibited from 19% (low dose) to 63% (high dose) in males and from 0 to 32% in females. In erythrocytes, ChE was inhibited from 27 (low dose) to 63% (high dose) in males and from 15 to 45% in females. Based on ChE inhibition, this study identified a Lowest-Observed-Adverse-Effect Level (LOAEL) of 10 mg/kg/day.

- Farbenfabriken Bayer (1966) conducted a 9-week feeding study with Bay 39007 (purity not specified) in male and female rats (Elberfeld FB30). Baygon was included in the diets of the male animals at dose levels of 0, 1,000, 2,000, 4,000 or 8,000 ppm. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 50, 100, 200 or 400 mg/kg/day, respectively. Females were given only one dose (4,000 ppm). The study was begun when the animals (15/dose level) were 4 weeks of age and weighed about 48 g. In males, food consumption and body weight were depressed in a dose-dependent manner. At the 4,000 and 8,000-ppm levels, the males were less lively and exhibited slightly shaggy coats. Gross pathologic examinations of all animals were conducted. Two males exposed to 4,000 ppm died during the study, one at 11 days (evidence of myocarditis) and one at 23 days. Two males also died at the 8,000-ppm level (at 23 and 25 days); one showed necrotic inflammation of the mucosa of the small intestine. Females (exposed to 4,000 ppm only) displayed decreased food consumption and reduced weight gain similar to that seen in exposed males. One of 15 female controls died at day 12 (death attributed to pneumonia), and two of 15 exposed females died, one at 7 days and one at 45 days (in this rat there was suppuration of the cerebellar bottom). There were apparently no measurements of ChE activity or other clinical tests performed during this study. It was concluded by the authors that the observed pathology could not be directly attributed to the presence of Baygon in the diet. Based on gross observations, the No-Observed-Adverse-Effect-Level (NOAEL) for male animals was identified as 2,000 ppm (100 mg/kg/day) and the LOAEL as 4,000 ppm (200 mg/kg/day). In females, 4,000 ppm (200 mg/kg/day, the only dose tested) was a toxic level.

- Eben and Kimmerle (1973) exposed SPF-Wistar rats (four/sex/dose) by gavage to doses of 3, 10 or 30 mg/kg/day of Baygon for 4 weeks. The high-dose animals (30 mg/kg/day) displayed cholinergic symptoms. Cholinesterase activity in plasma and red blood cells, measured 15 minutes after dosing on days 3, 8, 14, 21 and 28, was generally depressed in a dose-related manner at 10 and 30 mg/kg, but not at the 3-mg/kg dose. For example, on day 28, ChE activity in plasma was reduced by 0, 21 or 27% in males and by 14, 27 or 41% in females. In erythrocytes, ChE was inhibited by 9, 24 or 32% in males and by 11, 32 or 43% in females. No cumulative toxic effects were observed. Based on ChE inhibition, the NOAEL for this study was 3 mg/kg/day, and the LOAEL was 10 mg/kg/day.

Dermal/Ocular Effects

- The acute dermal LD_{50} of technical Baygon (purity not specified) was reported to be greater than 2,400 mg/kg for both male and female Sherman rats (Gaines, 1969).
- Crawford and Anderson (1971) indicated that 500 mg of technical Baygon (purity not specified, dissolved in acetone) did not cause any skin irritation within 72 hours of its application to the abraded or unabraded skin of mature New Zealand White rabbits (six/group).
- Heimann (1982) demonstrated that Baygon (98.8% pure) is not a skin sensitizer when tested in guinea pigs.
- Crawford and Anderson (1971) instilled 100 mg of technical Baygon (purity not specified) in the left eye of six rabbits. Examination at 48 and 72 hours revealed no evidence of ocular irritation or corneal damage.

Long-term Exposure

- Eben and Kimmerle (1973) fed propoxur (98.7% a.i.) to male SPF Wistar rats in the diet for 15 weeks. Doses were 0, 250, 750 or 2,000 ppm. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 12.5, 37.5 or 100 mg/kg/day. Assays for ChE activity in plasma, erythrocytes and brain showed no constancy of inhibition and no dependence on the administered dose. No other details were given.

- Root et al. (1963) studied the effect of Bayer 39007 added to the diet of Sprague-Dawley rats for 16 weeks. The rats (12/sex/dose, weighing 72 to 145 g at the start of the feeding trial) were fed Baygon (technical, 95.1% pure) at dose levels of 0, 100, 200, 400 or 800 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 5, 10, 20 or 40 mg/kg/day. Biweekly measurements revealed no changes in growth or food consumption. Cholinesterase was assayed in blood, brain and submaxillary glands of five animals of each sex at each dose level, and no inhibition was detected. Necropies were performed on five animals of each sex at the termination of the study, and no significant pathology was found. It was concluded that the NOAEL for the rats was greater than 800 ppm (40 mg/kg/day, the highest dose tested).

- Suberg and Loeser (1984) conducted a chronic (106-week) feeding study of Baygon (99.4% a.i.) in rats (Elberfeld strain) at dose levels of 0, 200, 1,000 or 5,000 ppm for 106 weeks. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 10, 50 or 250 mg/kg/day. There were 50 rats of each sex per dose level, plus an additional 10 of each sex for interim autopsies at the end of the first year. At the 200-ppm dose, there was no effect on food consumption or body weight, there were no cholinergic signs, and clinical chemistry, gross pathology, histopathology and organ weights showed no changes from control values. At 1,000 ppm, retarded weight gain was observed in males during the first 20 weeks. At 1,000 and 5,000 ppm, there were significant hyperplasia of urinary bladder epithelium (described in more detail in the Carcinogenicity section) and increased incidence of neuropathy. At the 5,000-ppm dose, both weight gain and food consumption were significantly retarded throughout the study; males showed increased thromboplastin time, and females had consistently lower mean plasma ChE activity than did controls or other test groups. No significant inhibition was reported in the examined dose group. Both sexes showed some degree of splenic atrophy, but there were no other significant changes in other organs. Based on body weight gain, the NOAEL for this study was identified as 200 ppm (10 mg/kg/day), and the LOAEL as 1,000 ppm (50 mg/kg/day).

- Loser (1968a) conducted a 2-year feeding study of Baygon in male and female SPF-Wistar rats (25/sex/dose). Starting at 1 month of age, the test material, BAY 39007 (99.8% a.i., technical), was included in the diet at levels of 0, 250, 750, 2,000 or 6,000 ppm. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day

(Lehman, 1959), this corresponds to doses of 0, 12.5, 37.5, 100 or 300 mg/kg/day. The control group consisted of 50 animals of each sex, while test groups contained 25 animals of each sex. Growth and behavior were observed, liver function and ChE activity were tested, and blood and urine were analyzed periodically. Necropsies on five animals of each sex were conducted at the termination of the experiment. The major adverse effects noted were low food consumption and low body weight in all animals at the 6,000-ppm dose level, and low body weight in the female (but not male) animals at the 2,000-ppm dose level. Cholinesterase determinations on blood (measured at the high dose only) revealed no changes; ChE activity was 9.8 and 9.9 units in control males and females, respectively, compared with 9.9 and 10.0 in exposed males and females. The author indicated that the methodology may have been too insensitive to detect small changes that may have occurred. No spasms or other symptoms of ChE inhibition were observed. No impairment of liver or kidney function was detected by clinical tests, but necropsy revealed increased liver weight at all doses greater than 250 ppm. Results of blood analysis were normal at all dose levels except at 6,000 ppm. Apart from increased liver weights, necropsy findings were unremarkable. Based on increased liver weights, this study identified a NOAEL of 250 ppm (12.5 mg/kg/day) and a LOAEL of 750 ppm (37.5 mg/kg/day).

- Loser (1968b) conducted a 2-year study of Baygon toxicity in beagle dogs (4/sex/dose). The product, BAY 39007 (technical, 99.8% pure), was included in the diet at levels of 0, 100, 250, 750 or 2,000 ppm. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 2.5, 6.25, 18.7 or 50 mg/kg/day. The study was begun when the dogs (four/sex/dose) were 4 to 5 months old. Observations on the animals included weight and food consumption at periodic intervals, ChE determinations in blood at 16 weeks, clinical evaluations of blood and urine, and tests for liver and kidney function. Necropsies were performed on animals that died during the study and at termination of the study. The appearance, behavior, and food consumption of dogs at the 100, 250 or 750 ppm levels were comparable to those of the controls. At the 2,000-ppm level, dogs of both sexes appeared to be weak and sick. One of the males and all four females at this dose died before completion of the study. During the first 6 months, dogs at this dose level exhibited quivering and spasms, particularly in the abdominal region, and food consumption was less than for the controls (especially in females); as expected, the dogs showed statistically significant depression in weight gain compared with the controls. Males, but not females, showed lower weights than did controls at the 750-ppm dose level, but the decrease was not statistically significant. Clinical analyses did not reveal any aberrations in the blood or any changes in liver or kidney function. However, increased liver weights were observed at necropsy, and serum electrophoresis performed at the time of sacrifice revealed decreased levels of some serum proteins, interpreted by the author as reflecting impaired protein synthesis. Cholinesterase determinations in whole blood at 16 weeks did not reveal any significant inhibition of activity. In males, ChE inhibition at 100, 250, 750 and 2,000 ppm was 0, 11, 1 and 13%, respectively, and in females ChE inhibition was 0, 10, 7 and 0%, respectively. The author indicated that the assay method may have been too insensitive to detect small changes that may have occurred. Emaciation was the principal finding in dogs that died during the study; one female had abnormal liver parenchyma. The NOAEL for this study was 250 ppm (6.25 mg/kg/day), and the LOAEL (based on increased liver weight, decreased body weight and altered blood proteins) was 750 ppm (18.7 mg/kg/day).

- Bomhard and Loeser (1981) conducted a 2-year feeding study of propoxur (99.6% a.i.) in SPF CF_1/W74 mice at dose levels of 0, 700, 2,000 or 6,000 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 105, 300 or 900 mg/kg/day. Mice were 5 to 6 weeks of age, weighing 22 to 25 g at the beginning of the study; each group consisted of 50 animals of each sex, plus an additional 10/sex/group included for interim autopsy at 1 year. Body weight gain was slightly depressed in male mice at the 6,000-ppm level. Apart from this observation, all aspects of behavior, appearance, food intake, weight and mortality were comparable to control values. Clinical chemistry and blood studies, including glucose and cholesterol levels, were within the normal range for all groups, and there were no significant gross pathological or histopathological findings that could be attributed to the ingestion of Baygon. It was concluded that the male mice tolerated the pesticide at levels up to and including 2,000 ppm, while the female mice tolerated doses up to and including 6,000 ppm without adverse effects. Based on these conclusions, the NOAEL for this study was 2,000 ppm (300 mg/kg/day), and the LOAEL (based on depressed weight gain in males) was 6,000 ppm (900 mg/kg/day).

Reproductive Effects

- No multigeneration studies of the effects of Baygon on reproductive function of animals were found in the available literature.
- In a developmental toxicity study in rabbits, Schlueter and Lorke (1981) observed no adverse effects on several reproductive end points. This study is described below.

Developmental Effects

- Schlueter and Lorke (1981) studied the effect of propoxur (99.6% a.i.) on Himalayan CHBB:HM rabbits during gestation. Propoxur was administered by gavage (in 0.5% cremophor) to 15 animals/dose at 0, 1, 3 or 10 mg/kg. No adverse effects were observed in the dams, and no changes were detected in implantation index, mean placental weight, resorption index or litter size. Embryos were examined for visceral and skeletal defects grossly, then were stained with Alizarin, and transverse sections were prepared using the Wilson technique. No adverse fetal effects were found at any dose level with respect to mean fetal weight, the percent of stunting, the percent of slight skeletal deviations, or the malformation index. These results indicate that the NOAEL for maternal toxicity, teratogenicity and fetotoxicity is greater than 10 mg/kg/day (the highest dose tested).

- Lorke (1971) fed Baygon (technical, 98.4% a.i., 0.82% isopropoxyphenol) in the diet to female FB-30 rats on days 1 to 20 of gestation, at levels of 0, 1,000, 3,000 or 10,000 ppm (10/dose). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, (Lehman, 1959), this corresponds to doses of about 50, 150 or 500 mg/kg/day. The rats were 2.5 to 3.5 months of age, weighing 200 to 250 g at the time of the experiment. Cesarean sections were performed on day 20. External and internal examinations on fetuses were performed, and fetuses were subjected to skeletal staining. At the 3,000- and 10,000-ppm dose levels, average fetal weights were significantly lower than control values, but other fetal measurements were in the control range. No terata were observed at a higher incidence than in the control group. Data on fetal ossification were not adequately described for an adequate evaluation. Although this study appears to reflect a NOAEL of 1,000 ppm (50 mg/kg/day) based on fetotoxic effects, information obtained from this study is limited due to the small number of animals tested and an apparent dose-related decrease in maternal weight gain and fetal weight at the lowest dose tested (although these effects were not statistically significant).

Mutagenicity

- DeLorenzo et al. (1978) evaluated the mutagenic properties of Baygon and other carbamate pesticides by use of the *Salmonella* mutagenicity test of Ames. In assays using five strains of *Salmonella typhimurium*, no mutagenic activity was obtained with Baygon at 10 to 1,500 ug/plate (with or without microsomal activation).

- Moriya et al. (1983) tested Baygon at up to 5,000 ug/plate in five strains of *S. typhimurium* and one strain of *Escherichia coli* using the Ames technique (without metabolic activation) and observed no evidence of mutagenic activity.

- Blevins et al. (1977) used five mutants of *S. typhimurium* LT2 to examine the mutagenic properties of Baygon and other methyl carbamates and their nitroso derivatives. No mutagenic activity was observed with Baygon in this experiment using the Ames technique.

Carcinogenicity

- Suberg and Loeser (1984) conducted a chronic (106-week) feeding study of Baygon (99.4% a.i.) in rats (Elberfeld strain SPF strain Bor. WISW) at dose levels of 0, 200, 1,000 or 5,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 10, 50 or 250 mg/kg/day. The study utilized 50 rats/sex/dose, plus an additional 10 of each sex included for interim necropsies at the end of the first year. At 5,000 ppm significant hyperplasia of the urinary bladder epithelium was noted. The incidence at this dose level after 2 years was 44/49 in males and 48/48 in females, as compared with 1/49 and 0/49 in control males and females, respectively. At 1,000 ppm, there was a smaller increased incidence (10/50 and 5/49 in males and females), respectively. No significant effect occurred at 200 ppm (1/50 and 0/49, males and females, respectively). Bladder papillomas were observed in both males (25/57) and females (28/48) at the highest dose after 2 years. In addition, at the 5,000-ppm level, carcinoma of the bladder was found in 8/57 males and 5/48 females, and carcinoma of the uterus was seen in 8/49 females, as compared with 3/49 for the control group. At the mid-dose level (1,000 ppm) only papillomas were noted in one male. The tumors of significance in this study are the uncommon bladder tumors (carcinoma and papillomas) with high incidences at the high dose level. The combined tumor incidences were 34/57 males and 33/48 females at 5,000 ppm; 1/59 males and 0/48 females at 1,000 ppm, and none in the 200-ppm or control groups.

- Bomhard and Loeser (1981) conducted a 2-year feeding study of propoxur (99.5% a.i.) in SPF CF_1/W74 mice at dose levels of 0, 700, 2,000 or 6,000 ppm. Assuming that 1 ppm in the diet is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 105, 300 or 900 mg/kg/day. Mice were 5 to 6 weeks of age, weighing 22 to 25 g at the beginning of the study; each group consisted of 50 animals of each sex, plus an additional 10/sex/group included for interim necropsy at 1 year. Gross and histological examination of tissues revealed no evidence of increased tumor frequency.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

whe-e:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The study by Vandekar et al. (1971) has been selected to serve as the basis for determination of the One-day HA for Baygon. In this study, human volunteers who ingested single oral doses of 0.36 or 1.5 mg/kg displayed transient cholinergic signs accompanied by marked (43 and 75%, respectively) inhibition of red blood cell ChE (measured 10 to 15 minutes after exposure). Total doses of 0.75 or 1.0 mg/kg administered in five equal portions over 2 hours did not cause clinical signs, but inhibited red blood cell ChE by about 40%. A NOAEL was not identified; 0.36 mg/kg is taken as the LOAEL for bolus exposure, and 0.45 mg/kg (three-fifths of a 0.75-mg/kg/day total dose, administered in the first 3/5 doses) is the LOAEL when exposure to this dose is spread over several hours. It should be noted that both values are considerably lower than the NOAEL values for Baygon identified in subchronic and chronic feeding studies in animals, especially rodents. Possible reasons for this disparity are that humans may be more sensitive to this chemical than animals are; furthermore, single oral doses probably produce higher peak inhibitions than if the same total dose is ingested over a longer period of time. It is also likely that measurement of ChE activity 10 to 15 minutes after exposure (as in the case of human studies) detects peak inhibition, while sampling later reveals smaller effects (due to the reversible nature of ChE inhibition with carbamates). Since a child's exposure is more likely to occur in a manner similar to Vandekar's test, where doses were administered in five equal portions over time, and since the LOAEL of 0.45 mg/kg (three-fifths of a 0.75 mg/kg total dose) caused a similar level of ChE inhibition as the bolus dose of 0.36 mg/kg (ChE inhibition is in the 40% range). Therefore, the LOAEL, 0.36 mg/kg is used for the calculation below:

The One-day HA for a 10-kg child is calculated as follows:

$$\text{One-day HA} = \frac{(0.36\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.036\ \text{mg/L}\ (40\ \text{ug/L})$$

where:

0.36 mg/kg/day = LOAEL, based on mild cholinergic signs and 43% inhibition of red blood cell ChE in humans 10 minutes after single oral dose.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from a human study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

In addition to human studies by Vandekar et al. (1971) discussed above, two studies were considered for determination of the Ten-day HA. In a teratology study in rabbits by Schlueter and Lorke (1981), the NOAEL appeared to be higher than 10 mg/kg/day, the highest dose tested. In a teratology study in rats by Lorke (1971), the dietary administration of Baygon to animals during gestation was designed to assess both maternal and fetal effects. While sufficient data were obtained to derive a NOAEL of 50 mg/kg/day and a LOAEL of 150 mg/kg/day in rats, it is important to note that a dosage of 50 mg/kg/day was sufficient to kill all female animals in a chronic study in dogs by Loser (1968b); all deaths occurred before the end of the 2-year study period. Because humans appear to be more sensitive to Baygon than animals, the human study by Vandekar et al. (1971), used in the determination of the One-day HA value, is also the most suitable study for calculation of the Ten-day HA. The two LOAELs identified in this study, 0.36 mg/kg (bolus exposure) and 0.45 mg/kg/day (exposure to three-fifths of a 0.75-mg/kg total dose spread out over the day) resulted in the same level of red blood cell ChE inhibition. Therefore, the lower dose, 0.36 mg/kg/day, is used for calculation of the Ten-day HA.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.36\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.036\ \text{mg/L}\quad (40\ \text{ug/L})$$

where:

0.36 mg/kg/day = LOAEL, based on mild cholinergic signs and 43% inhibition of red blood cell ChE in humans 10 minutes after a single oral dose.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from a human study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

No suitable information was found in the available literature for the determination of the Longer-term HA value for Baygon. It is, therefore, recommended that the modified Drinking Water Equivalent Level (DWEL) of 40 ug/L for a 10-kg child be used as a conservative estimate for a Longer-term exposure. The DWEL of 100 ug/L, calculated below, should be used for the Longer-term value for a 70-kg adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor. From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in dogs by Loser (1968b) and the human study by Vandekar et al. (1971) have been considered for determination of the Lifetime HA. In the 2-year dog study by Loser (1968b), the chronic NOAEL was identified as 6.25 mg/kg/day and the LOAEL as 18.7 mg/kg/day. The dog NOAEL value is supported by the data of Loser (1968a) and of Suberg and Loeser (1984), which identified NOAEL values of 12.5 and 10 mg/kg/day, respectively, in chronic studies in rats. However, the dog appears to be far more sensitive at the higher doses than are rodents; all female dogs and some of the males in the high-dose group, 50 mg/kg/day, died before the end of the study period, while mild systemic toxicity was noted at this dose level in rats. Cholinesterase determinations were not performed in the dog study for use in comparison with human data. Due to the reversible nature of ChE inhibition by carbamates, a large difference is noted between the dosages that can cause biologically significant levels of ChE inhibition and the dosages that can produce cholinergic symptoms of toxicity (including death). Hence, in the absence of ChE data in the dog study, and because of the sensitivity of this end point in the determination of the toxicity of this chemical, the study by Vandekar et al. (1971) in humans has been selected to serve as the basis for the Lifetime HA for Baygon. This study was discussed in the previous sections on the One-day and Ten-day HAs. The 2-year mouse study by Bomhard and Loeser (1981) was not considered, since the data suggest that the mouse is even less sensitive than the rat.

Using a human ChE LOAEL of 0.36 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.36 \text{ mg/kg/day})}{(100)} = 0.004 \text{ mg/kg/day}$$

(after rounding off from 0.0036 mg/kg/day)

where:

0.36 mg/kg/day = LOAEL, based on mild cholinergic signs and 43% inhibition of red blood cell ChE in a human 10 minutes after a single oral dose.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from a human study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.0036 \text{ mg/kg/day}) \ (70 \text{ kg})}{(2 \text{ L/day})} = 0.126 \text{ mg/L } (100 \text{ ug/L})$$

where:

0.0036 mg/kg/day = RfD (before rounding off to 0.004 mg/kg/day).

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(0.126\ \text{mg/L})\ (20\%)}{(10)} = 0.003\ \text{mg/L}\ (3\ \text{ug/L})$$

where:

0.126 mg/L = DWEL (before rounding off to 100 ug/L).

20% = assumed relative source contribution from water.

10 = additional uncertainty factor in accordance with ODW policy to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- Suberg and Loeser (1984) detected an increased frequency of urinary bladder epithelium hyperplasia, bladder papillomas and carcinomas, and carcinoma of the uterus in rats fed Baygon (250 mg/kg/day) for 2 years.

- Bomhard and Loeser (1981) did not detect an increased incidence of tumors in mice fed Baygon at doses up to 90 mg/kg/day for 2 years.

- The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenic potential of Baygon.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), Baygon may be classified in Group C: possible human carcinogen. This category is for substances with limited evidence of carcinogenicity in animals in the absence of human data. However, this classification group may be considered preliminary at the present (U.S. EPA, 1987b) since the U.S. EPA Office of Pesticide Programs (OPP) has classified this chemical in Group B2: probable human carcinogen (U.S. EPA, 1987a). A resolution will be reached between OPP and the Cancer Assessment Group (CAG) in the near future.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Residue tolerances have not been established for Baygon by the OPP.

- The American Conference of Governmental Industrial Hygienists (ACGIH, 1984) has proposed a threshold limit value of 0.5 mg/m^3.

- The World Health Organization (WHO) calculated an ADI of 0.02 mg/kg/day for Baygon (Vettorazzi and Van den Hurk, 1985).

VII. ANALYTICAL METHODS

- Analysis of Baygon is by a high-performance liquid chromatographic (HPLC) procedure used for the determination of N-methyl carbamoyloximes and N-methylcarbamates in water samples (U.S. EPA, 1986b). In this method 531.1 the water sample is filtered and a 400 uL aliquot is injected into a reverse-phase HPLC column. Separation of compounds is achieved using gradient elution chromatography. After elution from the HPLC column, the compounds are hydrolyzed with sodium hydroxide. The methyl amine formed during hydrolysis is reacted with o-phthalaldehyde (OPA) to form a fluorescent derivative that is detected with a fluorescence detector. This method has been validated in a single laboratory. The limit of detection for this method for Baygon is 1.0 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate granular activated carbon (GAC) adsorption to be a possible Baygon removal technique.

- Adsorption of Baygon on GAC proceeds in accordance with both Freundlich and Langmuir isotherms (El-Dib et al., 1974; Whittaker et al., 1982).

- One full-scale laboratory test was carried out on a commercially available system (Dennis et al., 1983; Kobylinski et al., 1984). Different levels of Baygon (20 mg/L, 60 mg/L and 100 mg/L) were added to tap water. At a flow rate of 67.4 gpm, the column removed 99% of the Baygon in 3.5, 8.5, and 21 hours, respectively, using only 45 lb of granular carbon.

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*Confidential Business Information submitted to the Office of Pesticide Programs

August, 1988

BENTAZON

Health Advisory
Office of Drinking Water
U.S Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

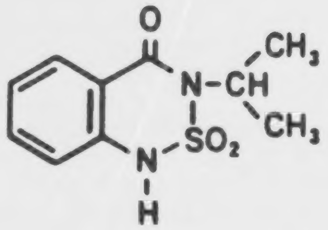
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 25057-89-0

Structural Formula



3-(1-Methylethyl)-1H-2,1,3-benzothiadiazin-4(3H)-one,2,2-dioxide

Synonyms

- Basagran; Bendioxide; Bentazone (Worthing, 1983).

Uses

- Selective postemergent herbicide used to control broadleaf weeds in soybeans, rice, corn, peanuts, dry beans, dry peas, snap beans for seed, green lima beans and mint (Meister, 1986).

Properties (Worthing, 1983)

Chemical Formula	$C_{10}H_{12}N_2O_3S$
Molecular Weight	240.3
Physical State	Colorless crystalline powder
Boiling Point	--
Melting Point	137 to 139°C
Density	--
Vapor Pressure	$<0.1 \times 10^{-7}$ mm Hg (20°C)
Water Solubility	500 mg/L
Specific Gravity	--
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Bentazon was not found in sampling performed at two water supply stations in the STORET database (STORET, 1988). No information on the occurrence of bentazon was found in the available literature.

Environmental Fate

- Bentazon, at 1 ppm, was stable to hydrolysis for up to 122 days in unbuffered water (initial pH 5, 7, and 9) at 22°C (Drescher, 1972c). The bentazon degradate, 2-amino-N-isopropyl benzamide (AIBA) at 1 ppm, was stable to hydrolysis in unbuffered, distilled water at pH 5, 7, and 9, during 28 days' incubation in the dark at 22°C (Drescher, 1973b).

- ^{14}C-Bentazon at 2 to 10 ppm, degraded with a half-life of less than 2 to 14 weeks in a sandy clay loam, loam, and three loamy sand soils (Drescher and Otto, 1973a; Drescher and Otto, 1973b). The soils were incubated at 14 to 72% of field capacity and 23°C. The bentazon degradation rate was not affected by soil moisture content but was decreased by lowering the temperatures to 8 to 10°C. At pH 6.4, the degradation rate in a loamy sand soil was 2.5 times longer than at pH 4.6 and 5.5. The bentazon degradate, AIBA, was identified at less than 0.1 ppm. AIBA degraded in loamy sand soil with a half-life of 1 to 10 days (43% of field capacity). ^{14}C-Bentazon at 1.7 ppm did not degrade appreciably in a loamy sand soil during 8 weeks of incubation; AIBA was detected at a maximum concentration of 0.008 ppm.

- Bentazon did not adsorb to Drummer silty clay loam, adjusted to pH 5 and 7, and 11 other soils tested at pH 5 (Abernathy and Wax, 1973). In the same study, using soil TLC, (^{14}C)bentazon was very mobile in 12 soils, ranging in texture from sand to silty clay loam, with an R_f value of 1.0.

- Bentazon was very mobile in a variety of soils, ranging in texture from loamy sand to silty clay loam and muck, based on soil column tests (Drescher and Otto, 1972; Abernathy and Wax, 1973; Drescher, 1973a; Drescher, 1972a). Approximately 73 to 103% of the bentazon applied to the columns was recovered in the leachate.

- AIBA (100 ug applied to loamy sand soil) was very mobile (Drescher, 1972b). After leaching a 12-inch soil column with 500 ml (10 inches) of distilled water, 86.3% of the applied material was found in the leachate.

- Bentazon has the potential to contaminate surface waters as a result of its mobility in runoff water and application to rice fields (Devine, 1972; Wuerzer, 1972).

- In the field, bentazon at 0.75 to 10 lb ai/A dissipated with a half-life of less than or equal to 1 month in the upper 6 inches of soil, ranging in texture from sand to clay (Daniels et al., 1976; Devine and Hanes, 1973; Stoner and Hanes, 1974b; Stoner and Hanes, 1974a; BASF Wyandotte Corporation, 1974; Devine and Tietjens, 1973; Devine et al., 1973). In the majority of soils (6 of 9), bentazon had a half-life of less than 7 days. AIBA was detected at less than or equal to 0.09 ppm. Collectively, the available data indicated that geographic region (NC, TX, MS, AL, MN, or ID) and crops treated (peanuts, soybeans, corn or fallow soil) had little or no effect on the dissipation rate of bentazon in soil.

III. PHARMACOKINETICS

Absorption

- Male and female rats (200 to 250 g) given 0.8 mg ^{14}C-bentazon in 1 mL of 50% ethanol by stomach tube excreted 91% of the administered dose in the urine within 24 hours. This suggests that bentazon is almost completely absorbed when ingested (Chasseaud et al., 1972).

Distribution

- Whole-body autoradiography of rats indicated high levels of radioactivity in the stomach, liver, heart and kidneys after 1 hour of dosing with ^{14}C-bentazon. Radioactivity was not observed in the brain or spinal cord (Chasseaud et al., 1972).

Metabolism

- Bentazon is poorly metabolized. Two unidentified metabolites were detected (Chasseaud et al., 1972).

Excretion

- Rats given radiolabeled bentazon excreted 91% of the administered dose in the urine as parent compound. Feces contained 0.9% of the administered dose (Chasseaud et al., 1972).

IV. HEALTH EFFECTS

Humans

- No information on the health effects of bentazon in humans was found in the available literature.

Animals

Short-term Exposure

- The oral LD_{50} of bentazon in the rat was reported to be 2,063 mg/kg (Meister, 1986).

- LD_{50} values for bentazon in the rat, dog, cat and rabbit are reported to be 1,100, 900, 500 and 750 mg/kg, respectively (RTECS, 1985).

Dermal/Ocular Effects

- Previously available information was invalidated. Therefore, it was not possible to utilize that information for the development of the Health Advisory.

Long-term Exposure

- Leuschner et al. (1970) reported the effects of bentazon in beagle dogs. Beagle dogs (three dogs/sex/dose) were given 0 (control), 100, 300, 1,000 and 3,000 ppm (0, 2.5, 7.5, 25 and 75 mg/kg/day; Lehman, 1959) of bentazon for 13 weeks. At a dose level of 3,000 ppm, overt signs of toxicity, including weight loss and ill health, were observed; 1/3 males and 2/3 females died. At 3,000 ppm, all males showed signs of prostatitis. Similar signs were observed in one male each at the 300- and 1,000-ppm levels. This study suggests a NOAEL of 100 ppm (2.5 mg/kg/day).

Reproductive Effects

- Previously available information was invalidated. Therefore, it was not possible to utilize that information for the development of the Health Advisory.

Developmental Effects

- Previously available information was invalidated. Therefore, it was not possible to utilize that information for the development of the Health Advisory.

Mutagenicity

- Previously available information was invalidated. Therefore, it was not possible to utilize that information for the development of the Health Advisory.

Carcinogenicity

- Previously available information was invalidated. Therefore, it was not possible to utilize that information for the development of the Health Advisory.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were found in the available literature that were suitable for determination of One-day HA values. It is, therefore, recommended that the Longer-term HA value for a 10-kg child (0.3 mg/L) be used at this time as a conservative estimate of the One-day HA.

Ten-day Health Advisory

No data were found in the available literature that were suitable for determination of Ten-day HA values. It is, therefore, recommended that the Longer-term HA value for a 10-kg child (0.3 mg/L) be used at this time as a conservative estimate of the Ten-day HA.

Longer-term Health Advisory

A 13-week study in beagle dogs has been selected for the calculation of a Longer-term HA (Leuschner et al., 1970). Beagle dogs (three dogs/sex/dose) were given 0 (control), 100, 300, 1,000 and 3,000 ppm (0, 2.5, 7.5, 25 and 75 mg/kg/day; Lehman, 1959) of bentazon for 13 weeks. At a dose level of 3,000 ppm, overt signs of toxicity, including weight loss and ill health, were observed; 1/3 males and 2/3 females died. At 3,000 ppm, all males showed signs of prostatitis. Similar signs were observed in one male each at the 300- and 1,000-ppm levels. This study suggests a NOAEL of 100 ppm (2.5 mg/kg/day).

Utilizing this NOAEL, a Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(2.5\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.25\ \text{mg/L}\ (300\ \text{ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of prostatic effects in dogs.

10 kg = assumed body weight of the child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(2.5\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 0.875\ \text{mg/L}\ (900\ \text{ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of prostatic effects in dogs.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986b), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Lifetime studies were not available to calculate a Lifetime HA. However, with the addition of another safety factor of 10 for studies of less-than-lifetime duration, the Lifetime HA may be calculated from the 13-week feeding study in dogs (Leuschner et al., 1970).

Using the NOAEL of 2.5 mg/kg/day, the Lifetime HA for bentazon is calculated as follows:

Step 1: Determination of a the Reference Dose (RfD)

$$\text{RfD} = \frac{(2.5\ \text{mg/kg/day})}{(1{,}000)} = 0.0025\ \text{mg/kg/day}$$

where:

2.5 mg/kg/day = NOAEL, based on the absence of prostatic effects in dogs.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.0025 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.0875 \text{ mg/L } (90 \text{ ug/L})$$

where:

0.0025 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.0875 \text{ mg/L})\ (20\%) = 0.0175 \text{ mg/L } (20 \text{ ug/L})$$

where:

0.0875 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No valid data are available to make a determination of the carcinogenic potential of bentazon.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), bentazon may be classified in Group D: not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- In response to a bentazon-tolerance review petition, EPA's Office of Pesticide Programs has concluded that "a tolerance cannot be supported at this time."

VII. ANALYTICAL METHODS

- Analysis of bentazon is by a gas chromatographic (GC) method applicable to the determination of bentazon in water samples (U.S. EPA, 1985). In this method, an aliquot of sample is acidified and extracted with ethyl acetate. The extract is dried, concentrated to 1 to 2 mL, and methylated with diazomethane. The methylated extracts are analyzed by gas chromatography with flame photometric detection. The method detection limit for bentazon has not been determined.

VIII. TREATMENT TECHNOLOGIES

- There is no information available regarding treatment technologies used to remove bentazon from contaminated water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

BROMACIL

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

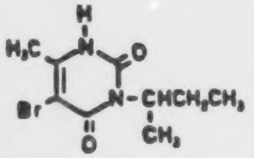
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No: 314-40-9

Structural Formula



5-Bromo-6-methyl-3-(1-methylpropyl)-2,4(1H,3H)-pyrimidinedione

Synonyms

- Borea; Bromax; Hyvar; Uragan; Urox B; (Meister, 1988).

Uses

- Herbicide for general weed or brush control in noncrop areas; particularly useful against perennial grasses (Meister, 1988).

Properties (Windholz et al., 1983)

Chemical Formula	$C_9H_{13}O_2N_2Br$
Molecular Weight	261.11
Physical State (at 25°C)	White crystalline solid
Boiling Point	--
Melting Point	158-160°C
Density	--
Vapor Pressure (100°C)	8×10^{-4} mm Hg
Specific Gravity	--
Water Solubility (20°C)	815 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Bromacil has been found in Florida ground water; a typical positive was 300 ppb (Cohen et al., 1986).

- Bromacil has not been found in any of 3 surface water samples collected at 2 locations or in any of 841 ground water samples collected at 834 locations (STORET, 1988). This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Bromacil in aqueous solution was stable when exposed to simulated sunlight for 6 days (Moilanen and Crosby, 1974). Only one minor (<4%) photolysis product (5-bromo-6-methyluracil) was identified. An aqueous solution of bromacil at 1 ppm lost all herbicidal activity after exposure to UV light for 10 minutes, but at 10 ppm and 15 minutes' irradiation herbicidal activity was still present (Kearney et al., 1964). However, bromacil in an aqueous solution (pH 9.4) containing the photosensitizer methylene blue was rapidly degraded under direct sunlight with a halflife of <1 hour (Acher and Dunkelblum, 1979).

- More than 26 soil fungi representative of several taxonomic groups, including Fungi Imperfecti, Ascomycetes and Zygomycetes, were capable of metabolizing bromacil as their sole carbon source (Wolf et al., 1975; Torgeson, 1969; Torgeson and Mee, 1967; Boyce Thompson Institute for Plant Research, 1971).

- Data from soil metabolism studies indicate that bromacil at 8 ppm had a half-life of about 6 months in aerobic loam soil incubated at 31°C (Zimdahl et al., 1970). However, 10% of applied bromacil at approximately 3 ppm was slowly degraded to CO_2 in an aerobic sandy loam soil after 330 days at 22°C (Wolf, 1974; Wolf and Martin, 1974). In anaerobic sandy loam soil, bromacil at approximately 3 ppm had a calculated half-life of approximately 144 days. No CO_2 evolved from the sterilized soil treated with bromacil within 145 days, indicating that degradation was microbial.

- Bromacil is mobile in soil. Phytotoxic residues of bromacil leached 19 cm in clay and silty clay loam soils eluted with the equivalent of 4.3 acre-inches of water (Signori et al., 1978). In mucky peat, loam and loamy sand soils eluted with the equivalent of 13 to 15 cm of water, bromacil leached to 10-, 25-, and to >30-cm depths, respectively (Day, 1976). Utilizing soil thin-layer chromatographic techniques ^{14}C-bromacil was evaluated to be mobile (R_f 0.7) in a silty clay loam soil (Helling, 1971). Bromacil is not adsorbed by montmorillonite, illite, or humic acid to any great extent [Freundlich K (adsorption coefficient) ≤10 at 25°C]; however, at 0°C bromacil was adsorbed (Freundlich K 126) to humic acid (Haque and Coshow, 1971; Volk, 1972). Adsorption appeared to increase with decreasing temperatures.

- Data from field dissipation studies showed that bromacil phytotoxic residues persisted in soils ranging in texture from sand to clay for >2 years following a single application of bromacil at ≥2.6 lb ai/A (active ingredient/acre) (Bunker et al., 1971; Stecko, 1971).

III. PHARMACOKINETICS

Absorption

- Workers who were exposed to bromacil during production, formulation and packaging excreted unchanged bromacil and the 5-bromo-3-sec-butyl-6-hydroxymethyluracil metabolite in the urine (DuPont, 1966b). Unchanged bromacil and the metabolite were also detected in the urine of rats fed bromacil in the diet (DuPont, 1966a). Although these data indicate that bromacil is absorbed, sufficient information was not available to quantify the extent of absorption.

Distribution

- No information was found in the available literature on the distribution of bromacil.

Metabolism

- Workers at a bromacil production plant excreted unchanged bromacil and the 5-bromo-3-sec-butyl-6-hydroxymethyluracil metabolite, present as the glucuronide and/or sulfonate conjugate, in urine (DuPont, 1966b).

- Gardiner et al. (1969) fed rats (age and strain not specified) food containing 1,250 ppm bromacil for 4 weeks. Assuming 1 ppm equals 0.05 mg/kg/day in the older rat (Lehman, 1959), this dietary level corresponds to about 62.5 mg/kg/day. Analysis of the urine of these rats revealed the presence of unchanged bromacil and the 5-bromo-3-sec-butyl-6-hydroxymethyluracil metabolite (primarily as the glucuronide and/or sulfonate conjugate). Five other minor metabolites were also detected: 5-bromo-3-(2-hydroxy-1-methylpropyl)-6-methyluracil; 5-bromo-3-(2-hydroxy-1-methylpropyl)-6-hydroxymethyluracil; 3-sec-butyl-6-hydroxymethyluracil; 5-bromo-3-(3-hydroxyl-1-methylpropyl)6-methyluracil; and 3-sec-butyl-6-methyluracil. An unidentified bromine-containing compound with a molecular weight of 339 was also detected.

Excretion

- In humans exposed to bromacil during its formulation and packaging, urinary excretion products included 0.1 ppm parent compound and 6.3 ppm 5-bromo-3-sec-butyl-6-hydroxymethyluracil, present mostly as a conjugate (DuPont, 1966b).

- Rats were fed bromacil (1,250 ppm in the diet) for 4 weeks; urine was collected daily during weeks 3 and 4 of the study. Analysis of the urine revealed the presence of 20 ppm unchanged bromacil and 146 ppm of the 5-bromo-3-sec-butyl-6-hydroxymethyluracil metabolite (conjugated and unconjugated form) (DuPont, 1966a; Gardiner et al., 1969).

IV. HEALTH EFFECTS

Humans

- No information was located in the available literature on the health effects of bromacil in humans.

Animals

- Most of the animal data available are from unpublished studies identified prior to the published report by Sherman and Kaplan (1975). These authors stated that an 80% wettable bromacil powder was used in all tests discussed in their report except for eye irritation studies in which a 50% wettable bromacil powder was used. All dosages and feeding levels, unless otherwise stated, were based on the active ingredient, bromacil.

Short-term Exposure

- The oral LD_{50} value for male ChR-CD rats was calculated to be 5,200 mg/kg (Sherman and Kaplan, 1975). Clinical signs of toxicity included rapid respiration, prostration and initial weight loss.

- In one male mongrel dog, a single oral dose in capsules of 5,000 mg/kg caused nausea, vomiting, fatigue, incoordination and diarrhea (Sherman and Kaplan, 1975). It was not possible to estimate a lethal oral dose for bromacil in dogs because vomiting occurred almost immediately in another dog at doses of 100 or 250 mg/kg given 5 days apart.

- Sherman and Kaplan (1975) administered bromacil to groups of six male ChR-CD rats by gastric intubation at dose levels of 650, 1,035 or 1,500 mg/kg/day, 5 days/week for 2 weeks (10 doses). Four of six animals died at the high dose. Five of six survived exposure to 1,035 mg/kg/day, but showed gastrointestinal and nervous system disturbances, and there was focal liver cell hypertrophy and hyperplasia. All animals survived the low dose with similar, but less severe, pathological changes. The 650-mg/kg/day dose is identified as the Lowest-Observed-Adverse-Effect-Levels (LOAEL) in this study.

- Palmer (1964) reported that sheep that received bromacil at oral doses of 250 mg/kg for five days developed weakness in the legs and incoordination. Recovery from these symptoms usually took several weeks. Administration of 100 mg/kg/day for 11 days induced an 11% weight loss but no observable clinical symptoms.

Dermal/Ocular Effects

- Bromacil (applied as a 50% aqueous solution of the 80% wettable powder) was only mildly irritating to the intact and abraded skin of young guinea pigs exposed for periods of up to 3 weeks. It was more irritating to the skin of older animals. Bromacil did not produce skin sensitization (DuPont, 1962).

- Sherman and Kaplan (1975) reported that when bromacil was applied dermally to rabbits the lethal dose was greater than 5,000 mg/kg, the maximum feasible dose. No clinical signs of toxicity and no gross pathological changes were observed.

- Bromacil, as a 50% aqueous suspension, was mildly irritating to the skin of young guinea pigs, but only slightly more irritating to the skin of older animals. It was not a skin sensitizer (Sherman and Kaplan, 1975).

- Sherman and Kaplan (1975) reported that bromacil (0.1 mL of a 10% suspension in mineral oil) resulted in only mild temporary conjunctivitis in both the washed and unwashed eyes of rabbits. No corneal injury was observed when a dose of 10 mg dry powder was applied directly to the eye.

Long-term Exposure

- Zapp (1965) discussed a study, also reported by Sherman and Kaplan (1975), in which 10 male and 10 female ChR-CD rats were fed dietary levels of 0, 50, 500 or 2,500 ppm bromacil for 90 days. This corresponds to doses of about 0, 2.5, 25 or 125 mg/kg/day, assuming 1 ppm equals 0.05 mg/kg/day in an older rat (Lehman, 1959). Because no signs of toxicity were observed at any dose, the high dose was increased to 5,000 ppm (about 250 mg/kg/day) after 6 weeks; to 6,000 ppm (about 300 mg/kg/day) after 10 weeks; and to 7,500 ppm (about 375 mg/kg/day) after 11 weeks. This dosing pattern resulted in reduced food intake and mild histological changes in thyroid and liver. No compound-related effects on weight gain, hematology, urinalysis or histology were detected at the two lowest doses; 25 mg/kg/day was identified as the No-Observed-Adverse-Effect Level (NOAEL) in this study.

- Sherman et al. (1966, also reported by Sherman and Kaplan, 1975) fed groups of 36 male and 36 female ChR-CD rats food containing 0, 50, 250 or 1,250 ppm bromacil for 2 years. This corresponds to doses of about 0, 2.5, 12.5 or 62.5 mg/kg/day, assuming 1 ppm equals 0.05 mg/kg/day in older rats (Lehman, 1959). Females at the highest dose showed decreased weight gain ($p < 0.001$). No other toxic effects were observed in a variety of parameters measured, including mortality, hematology, urinalysis, serum biochemistry, gross pathology, organ weight or histopathology, except for a slight thyroid hyperplasia at the high dose. This study identified a NOAEL of 12.5 mg/kg/day.

- Beagle dogs (three/sex/dose level) were fed a nutritionally complete diet containing 0, 50, 250 or 1,250 ppm bromacil for 2 years (Sherman et al., 1966; also reported by Sherman and Kaplan, 1975). This corresponds to doses of about 0, 1.25, 6.25 or 31.2 mg/kg/day, assuming 1 ppm equals 0.025 mg/kg/day in the dog (Lehman, 1959). No nutritional, clinical, hematological, urinary, blood chemistry or histopathologic evidence of toxicity was detected in any group. This study identified a NOAEL of 31.2 mg/kg/day.

- Kaplan et al. (1980) administered bromacil (approximately 95% pure) to CD-1 mice (80/sex/dose) for 78 weeks at dietary levels of 0, 250, 1,250 or 5,000 ppm. Based on information presented by the authors, these dietary levels correspond to doses of 0, 39.6, 195 or 871 mg/kg/day for males and 0, 66.5, 329 or 1,310 mg/kg/day for females. During the first year of the study, a compound-related decrease in body weight gain was observed in male mice receiving 5,000 ppm and in female mice receiving 1,250 ppm. The treatment and control groups exhibited no significant ($p < 0.05$) differences in food consumption. Mortality in the 5,000-ppm females was significantly ($p < 0.05$) greater than in the controls. Liver changes noted in treated mice consisted of increased mean and relative weights in the 1,250-ppm females and the 5,000-ppm males; an increased incidence of diffuse hepatocellular hypertrophy in the 1,250- and 5,000-ppm males and in the 5,000-ppm females; an increased incidence of centrilobular vacuolation in 250-ppm males; an increased incidence of scattered hepatocellular necrosis in 5,000-ppm males; and the presence of extravasated erythrocytes in the hypertrophied hepatocytes of the 1,250- and 5,000-ppm males. The authors felt that centrilobular vacuolation and hypertrophy were probably related to enzyme induction. The toxicological significance of extravasated erythrocytes in the hypertrophied hepatocytes was unclear. Compound-related changes in the testes of mice consisted of an increased incidence of spermatocyte necrosis, sperm calculi and mild interstitial-cell hypertrophy/hyperplasia in the 1,250- and 5,000-ppm males and a dose-related increase in the incidence of testicular tubule atrophy in all male treatment groups. Based on changes in testes, a LOAEL of 250 ppm (39.6 mg/kg/day) is identified for male mice. A NOAEL of 250 ppm (66.5 mg/kg/day) was identified for female mice.

Reproductive Effects

- Sherman et al. (1966; also reported by Sherman and Kaplan, 1975) reported the effects of bromacil on reproduction in a three-generation study in rats. Twelve male and twelve female weanling ChR-CD rats were fed bromacil in the diet at 0 or 250 ppm. This corresponds to doses of about 0 or 12.5 mg/kg/day, assuming 1 ppm in the diet equals 0.05 mg/kg/day for older rats (Lehman, 1959). Animals were bred after 12 weeks, and the F_{1b} and the F_{2b} generations were maintained on the same diets as their parents. No evidence of adverse effects on reproduction or lactation performance was observed. Examination of the F_{2b} generation revealed no evidence of gross or histopathological effects. This study identified a minimum NOAEL of 12.5 mg/kg/day.

Developmental Effects

- Paynter (1966; also reported by Sherman and Kaplan, 1975) administered bromacil to New Zealand White rabbits (8 or 9 per dosage) at dietary levels of 0, 50 or 250 ppm on days 8 through 16 of gestation. Assuming 1 ppm equals 0.03 mg/kg/day in the rabbit (Lehman, 1959), these dietary levels correspond to about 0, 1.5 or 7.5 mg/kg/day. No significant differences between the conception rates of the control and test groups were observed. Control and test group litters were comparable in terms of litter size, mean pup length, mean litter weight, number of stillbirths and number of resorption sites. No gross malformations were observed in any animals. Skeletal clearing revealed no abnormalities in bone structure in any animals. Based on reproductive and teratogenic end points, a NOAEL of 250 ppm (7.5 mg/kg/day) was identified.

- Pregnant rats (strain not specified) were exposed to aerosols of bromacil (165 mg/m^3) on days 7 to 14 of gestation. No prenatal changes or teratogenic effects were observed (no further details were provided) (Dilley et al., 1977).

Mutagenicity

- In a sex-linked recessive lethal test (Valencia, 1981), *Drosophila melanogaster* (Canton-S wild-type stock) were exposed to bromacil in food at levels of 2, 3, 5 or 2,000 ppm. Bromacil was found to be weakly mutagenic at the 2,000-ppm dose level.

- Riccio et al. (1981) reported that bromacil (tested concentrations not specified) was not mutagenic with or without metabolic activation in assays conducted using *Saccharomyces cerevisiae* strains D3 and D7.

- Siebert and Lemperle (1974) reported that bromacil was not mutagenic when tested at a concentration of 1,000 ppm using *S. cerevisiae* strain D4.

- Simmon et al. (1977) reported that bromacil was not mutagenic in an *in vivo* mouse dominant-lethal assay and the following *in vitro* assays: unscheduled DNA synthesis in human fibroblasts (WI-38 cells); reverse mutation in *Salmonella typhimurium* strains TA1535, 1537, 1538 and 100, and in *Escherichia coli* WP2; mitotic recombination in *S. cerevisiae*; and preferential toxicity assays in *E. coli* (strains W3110 and p3478) and *Bacillus subtilis* (strains H17 and M45).

- In a modified Ames assay (Rashid, 1974), bromacil was not mutagenic in *S. typhimurium* strains TA1535 and 1538 when tested at concentrations up to 325 ug/plate.

- In an assay designed to test for thymine replacement in mouse DNA (McGahen and Hoffman, 1963), Swiss-Webster white mice received bromacil by oral intubation at 100 mg/kg twice daily for 2 days, followed by 50 mg/kg twice daily for 8 days. Under the conditions of the assay, bromacil was not recognized as a thymine analog by the mouse.

- Bromacil did not show any signs of mutagenicity in a variety of microbial test systems (Jorgenson et al., 1976; Woodruff et al., 1984).

- In the Ames test, bromacil (5% concentration) induced revertants in three of six *Salmonella* strains tested (Njage and Gopalan, 1980).

- Bromacil did not induce sex-linked recessive lethals in *D. melanogaster* (Gopalan and Njage, 1981).

Carcinogenicity

- Sherman et al. (1966) fed groups of 36 male and 36 female weanling ChR-CD rats bromacil in the diet for 2 years. Dietary levels were 0, 50, 250 or 1,250 ppm (about 0, 2.5, 12.5 or 62.5 mg/kg/day, based on Lehman, 1959). There was no effect on mortality, and the only treatment-related lesion detected by histological examination was a slight increase in the incidence of light-cell and follicular-cell hyperplasia in the thyroid at the high dose. One high-dose female was found to have follicular-cell adenoma.

- Kaplan et al. (1980) administered bromacil (approximately 95% pure) to CD-1 mice (80/sex/dose) for 78 weeks at dietary levels of 0, 250, 1,250 or 5,000 ppm. Based on information presented by the authors, these dietary levels correspond to compound intake levels of 0, 39.6, 195 or 871 mg/kg/day for males and 0, 66.5, 329 or 1,310 mg/kg/day for females. In males, the combined incidences of hepatocellular adenomas plus carcinomas/number of animals examined were 10/74, 11/71, 8/71 and 19/70 ($p < 0.05$) at 0, 250, 1,250 and 5,000 ppm, respectively. Hepatocellular carcinoma incidences were 5/74, 4/71, 4/71 and 9/70 ($p > 0.05$) at 0, 250, 1,250 and 5,000 ppm, respectively. These tumors were found predominantly in mice that survived to terminal sacrifice. No effect on liver tumor incidence was observed in females.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No studies were located which are suitable for derivation of a One-day HA for bromacil. The acute dosing study in dogs reported by Sherman and Kaplan

(1975) is not considered because the bolus treatment with 100 mg/kg by capsule could be an inaccurate indication of the ability of this species to tolerate more divided doses as in diet or drinking water, as suggested by the 31.2 mg/kg/day NOAEL in the 2-year study in dogs by Sherman et al. (1966). Ten-day HA, derived below, of 5 mg/L for a 10-kg child is proposed as a conservative One-day HA.

Ten-day Health Advisory

The 2-week oral study in rats by Sherman and Kaplan (1975) has been selected as the basis for the Ten-day HA for bromacil. Animals were dosed by gavage for 10 days over a period of 2 weeks. The lowest dose tested (650 mg/kg/day) produced mild pathological changes in the liver, and this value was identified as a LOAEL. Although a lower oral LOAEL of 100 mg/kg was evident in sheep (Palmer, 1964), this study was not selected for HA development because of uncertainty in using ruminants in estimating risk to humans from oral exposure.

Using a LOAEL of 650 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(650\ \text{mg/kg/day})\ (5/7)\ (10\ \text{kg})}{(1{,}000)\ (1\ \text{L/day})} = 4.6\ \text{mg/L}\ (5{,}000\ \text{ug/L})$$

where:

650 mg/kg/day = LOAEL, based on mild liver pathology in rats exposed by gavage to bromacil for 2 weeks.

5/7 = correction for dosing 5 days per week.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The 90-day study by Zapp (1965) has been selected to serve as the basis for the Longer-term HA for bromacil. Rats were fed diets containing up to 500 ppm without any adverse effects. This study identified a NOAEL of 500 ppm (about 25 mg/kg/day).

Using a NOAEL of 25 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(25\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 2.5\ \text{mg/L}\ (3{,}000\ \text{ug/L})$$

where:

25 mg/kg/day = NOAEL, based on the absence of any pathological evidence of toxicity in rats exposed to bromacil via oral feeding for 90 days.

10 kg = assumed body weight of child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Using a NOAEL of 25 mg/kg/day, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(25\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 8.8\ \text{mg/L}\ (9{,}000\ \text{ug/L})$$

where:

25 mg/kg/day = NOAEL, based on absence of any toxic effects in rats exposed to bromacil via oral feeding for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The chronic feeding study in rats by Sherman et al. (1966) has been selected to serve as the basis for the Lifetime HA. This study identified a dietary LOAEL of 1,250 ppm and a NOAEL of 250 ppm, based on weight gain and mild thyroid hyperplasia. This NOAEL corresponds to 12.5 mg/kg/day. The same NOAEL is evident in a three-generation reproduction study in rats by Sherman et al. (1966). The long-term feeding studies in dogs by Sherman et al. (1966) and mice by Kaplan et al. (1980) were not selected, since the demonstrated NOAEL was the lowest in the rat study.

Using a NOAEL of 12.5 mg/kg/day, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(12.5\ \text{mg/kg/day})}{(100)} = 0.125\ \text{mg/kg/day}$$

(rounded to 0.13 mg/kg/day)

where:

12.5 mg/kg/day = NOAEL, based on absence of hepatic effects in rats exposed to bromacil via the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.13\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 4.55\ \text{mg/L}\ (5{,}000\ \text{ug/L})$$

where:

0.13 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(4.6\ \text{mg/L})\ (20\%)}{10} = 0.09\ \text{mg/L}\ (90\ \text{ug/L})$$

where:

4.6 mg/L = Lifetime HA at 100% contribution from drinking water.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy for use with a Group C carcinogen.

Evaluation of Carcinogenic Potential

- Bromacil has not been determined to be carcinogenic, although an increased incidence of hepatocellular adenomas plus carcinomas was observed in male but not female CD-1 mice fed bromacil in the diet at a dose level of 871 mg/kg/day for 78 weeks (Kaplan et al., 1980).

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of bromacil.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), bromacil is classified in Group C: possible human carcinogen. This category is for substances with limited evidence of carcinogenicity in animals in the absence of human data.

- The U.S. EPA has not published excess lifetime cancer risks for this material.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The NAS (1977) has calculated an acceptable daily intake (ADI) of 0.0125 mg/kg/day, based on a chronic NOAEL of 12.5 mg/kg/day in rats and an uncertainty factor of 1,000. A suggested-no-adverse-response level (SNARL) of 0.088 mg/L was calculated based on an assumed water consumption of 2 L/day by a 70-kg adult, with 20% contribution from water.

- The U.S. EPA Office of Pesticide Programs (EPA/OPP) previously calculated an ADI of 62.5 ug/kg/day, based on a NOAEL of 6.25 mg/kg/day in a 2-year feeding study in dogs (Sherman et al., 1966) and an uncertainty factor of 100. This was updated to 130 ug/kg/day based on a 2-year rat feeding study using a NOAEL of 12.5 mg/kg/day and a 100-fold uncertainty factor.

- A tolerance of 0.1 ppm bromacil in or on citrus fruits and pineapples has been set by the EPA/OPP (CFR, 1985). A tolerance is a derived value based on residue levels, toxicity data, food consumption levels, hazard evaluation and scientific judgment, and it is the legal maximum concentration of a pesticide in or on a raw agricultural commodity or other human or animal food (Paynter et al., undated).

- The American Conference of Governmental Industrial Hygienists (ACGIH, 1984) has recommended a threshold limit value (TLV) of 1 ppm, and a short-term exposure limit (STEL) of 2 ppm.

VII. ANALYTICAL METHODS

- Analysis of bromacil is by a gas chromatographic (GC) method applicable to the determination of certain organonitrogen pesticides in water samples (U.S. EPA, 1988). This method requires a solvent extraction of approximately 1 liter of sample with methylene chloride using a separatory funnel. The methylene chloride extract is dried and exchanged to acetone during concentration to a volume of 10 mL or less. The compounds in the extract are separated by gas chromatography and measurement is made with a thermionic bead detector. This method has been validated in a single laboratory, and estimated detection limits have been determined for the analytes in the method, including bromacil. The estimated detection limit is 2.5 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information was found in the available literature on treatment technologies used to remove bromacil from contaminated water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

BUTYLATE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

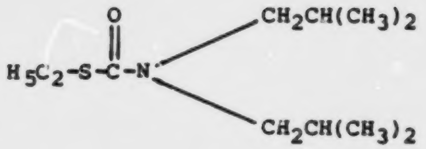
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 2008-41-5

Structural Formula



Carbamothioic acid, bis(2-methylpropyl)-, S-ethyl ester

Synonyms

- S-ethyl di-isobutylthiocarbamate; S-ethyl bis(2-methylpropyl) carbamothioate; ethyl N,N-di-isobutyl thiocarbamate; S-ethyl-di-isobutyl thiocarbamate; ethyl-N,N-di-isobutyl thiolcarbamate; R-1910; Sutan®+; Anelda Plus; Genate Plus (Meister, 1988).

Uses

- Selective preplant herbicide (Meister, 1988).

Properties (BCPC, 1977)

Chemical Formula	$C_{11}H_{23}NOS$
Molecular Weight	217.41
Physical State (25°C)	Clear liquid, aromatic odor
Boiling Point	138°C
Melting Point	--
Density (25°C)	0.9417
Vapor Pressure (25°C)	1.3×10^{-3} mm Hg
Specific Gravity	--
Water Solubility (20°C)	45 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Butylate has been found in 91 of 836 surface water samples analyzed and in 2 of 152 ground water samples (STORET, 1988). Samples were collected at 80 surface water locations and 61 ground water locations, and butylate was found in 5 states. The 85th percentile of all nonzero samples was 0.17 ug/L in surface water and 138,000 ug/L in ground water sources. The maximum concentration found was 4.70 ug/L in surface water and 138,000 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Butylate degrades fairly rapidly in moist soils under aerobic conditions; half-lives were 3 to 10 weeks (Thomas and Holt, 1979; Shell Development Company, 1975; Stauffer Chemical Company, 1975a). Under anaerobic conditions, butylate degrades with a half-life of 13 weeks (Thomas et al., 1978). Butylate sulfoxide is the major degradate, but S-ethyl-2,2-dimethyl-2-hydroxyethylisobutyl thiocarbamate, diisobutylformamide, diisobutylamine, diisobutylthiocarbamate, and isobutylamine were also identified as degradates (Thomas and Holt, 1979; Thomas et al., 1978; Shell Development Company, 1975; Stauffer Chemical Company, 1975a).

- Butylate is slightly mobile to highly mobile in soils ranging in texture from silty clay loam to gravelly sand (Gray and Weierich, 1966; Lavy, 1974; Thomas and Holt, 1979; Weidner, 1974).

- Butylate is fairly volatile; 45 to 50% of ^{14}C- butylate applied to moist (20% moisture) Sorrento clay loam was recovered as volatile radioactivity over 3 weeks following treatment. Volatile radioactivity was characterized as butylate (Thomas and Holt, 1979).

- In the field, butylate dissipated more readily in a soil in Florida than in a silty clay loam in California, probably leaching beyond the 6-inch sampling depth. The estimated half-lives in the upper 6 inches of the sand were 28 and 18 days when a 4 lb/gal Mcap and a 6.7 lb/gal EC formulation, respectively, were applied at 8 lb ai/A. For the silty clay loam, estimated half-lives were more than 64 days for both the Mcap and a 7 lb/gal EC formulation applied at 8 lb ai/A (active ingredient/acre) (Stauffer Chemical Company, 1975b; Stauffer Chemical Company, 1975c).

- Butylate has a low bioaccumulation potential in bluegill sunfish. A bioconcentration factor of 33 was found in the edible portion of fish dosed with ^{14}C-butylate at 0.01 or 1 ppm for 28 days. The nonedible portion of fish dosed at 0.01 and 1 ppm exhibited bioconcentration factors of 174 and 122, respectively. After 10 days of depuration, 50 to 67% of the day-28 residues was lost (Sleight, 1973).

III. PHARMACOKINETICS

Absorption

- Data relating specifically to the absorption of butylate were not located in the available literature; however, some information was obtained from a metabolism study by Hubbell and Casida (1977). Doses of 12.3 or 156.0 mg/kg ^{14}CO-labeled butylate were administered by gavage to male albino Sprague-Dawley rats weighing 190 to 210 g. Within 48 hours, 27.3 and 31.5% of the administered radioactivity were recovered in the urine, and 60.9 and 64.0% were expired as $^{14}CO_2$ in the low- and high-dose groups, respectively. These results indicate that butylate is appreciably absorbed from the gastrointestinal tract of rats.

Distribution

- Hubbell and Casida (1977) measured the tissue radioactivity 48 hours after the administration by gavage of 12.3 or 156.0 mg ^{14}CO-labeled butylate/kg to male Sprague-Dawley rats. At the low dose, 2.4% of the administered radioactivity was retained in the body, with levels of radioactivity equivalent to 276 ppb in the blood, 524 ppb in the kidney, 710 ppb in the liver and a range of 182 to 545 ppb in other tissues (brain, fat, heart, lung, muscle, spleen and testes). At the high dose, 2.2% of the radioactivity was retained in the body with 2,076 ppb in the blood, 5,320 ppb in the kidney, 7,720 ppb in the liver and 1,720 to 5,560 ppb in other tissues.

Metabolism

- Hubbell and Casida (1977) followed the metabolism of butylate in male Sprague-Dawley rats based upon identification of the 48-hour urinary metabolites of ^{14}CO-labeled preparations of butylate (12.3 or 156 mg/kg). Degradation of administered butylate metabolites was also assessed. Approximately 40% of the administered ^{14}CO-butylate was metabolized by ester cleavage and $^{14}CO_2$ liberation without going through the sulfoxide (the major metabolite) as an intermediate. The metabolites from all compounds were essentially the same qualitatively and quantitatively. The metabolites for ^{14}CO-butylate included, as percent of urinary radioactivity, 4.3% as the N,N-di-isobutyl mercapturic acid, 17.1% as the N-isobutylmercapturic acid, 0.8% as the mercaptoacetic acid derivative, 11.7% as the glycine conjugate of the mercaptoacetic acid derivative and about 66% as at least 15 other metabolites.

- S-(1-^{14}C)ethyl-Sutan®, orally administered at about 110 mg Sutan®/kg, was readily degraded and excreted by male and female Sprague-Dawley rats (Thomas et al., 1980). Cleavage of the S-ethyl moiety and the incorporation of the two-carbon fragment into intermediary metabolic pathways accounted for >70% of the total administered radiocarbon. Urinary excretion of ^{14}C-hippuric acid, ethyl methyl sulfoxide and ethyl methyl sulfone was evident.

Excretion

- Hubbell and Casida (1977) administered 12.3 or 156 mg/kg of ^{14}CO-labeled butylate by gavage to adult male Sprague-Dawley rats. Within 24 hours, 60.9 and 64.0% of the administered radioactivity were expired as CO_2, 27.3 and 31.5% were excreted in the urine and 3.3 and 4.7% were excreted in the feces in the low- and high-dose groups, respectively.

- A study by Bova et al. (1978) indicates that biotransformation of S-($1-{}^{14}C$) ethyl-Sutan® in male and female Sprague-Dawley rats given oral doses of 83.5 to 133.5 mg Sutan®/kg involves rapid cleavage of the S-ethyl moiety. Degradation of this fragment of the molecule results in the release of ${}^{14}CO_2$ as the major product of metabolism, accounting for 69% of the total administered dose. This rapid production of ${}^{14}CO_2$ may account for the relatively high levels (7.8%) of ${}^{14}C$ found in the tissues after 8 days. Urine and feces accounted for 13.9 and 3.2% of the ${}^{14}C$ dose, respectively.

- Data obtained from a 3-day balance and tissue residue study by Thomas et al. (1979) show that ($1-{}^{14}C$-isobutyl)Sutan® is readily eliminated by male and female Sprague-Dawley rats after a single oral dose (about 100 mg Sutan®/kg). More than 99% of the administered radiocarbon was recovered from the animals within 72 hours after dosing. Most of the dose (94%) was recovered within 24 hours after treatment. Less than 0.5% of the radiocarbon remained in the tissues after 72 hours, and the Sutan® equivalents in organ and tissue samples were all less than 2 ppm. Urine, feces and expired ${}^{14}CO_2$ accounted for 93.7, 4.0 and 2.0% of the dose, respectively.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of butylate in humans.

Animals

Short-term Exposure

- The acute oral LD_{50} value in male and female rats given butylate technical (85.71% pure) was 3.34 and 3.0 g/kg, respectively (Raltech, 1979).

Dermal/Ocular Effects

- Skin irritation was observed in rabbits topically exposed to 2 g butylate technical (85.71% pure) for 24 hours (Raltech, 1979).

- Topical application of R-1910 6E technical (97.5% pure) at doses of 20 and 40 mg active ingredient (a.i.)/kg, 5 days per week for a total of 21 applications, was without observed effect except for local skin irritation (Woodard Research Corp., 1967a).

- Application of butylate technical (85.71% pure) to the eyes of rabbits resulted in irritation and corneal opacity. No corneal opacity was in eyes washed after treatment (Raltech, 1979).

Long-term Exposure

- Dietary feeding of R-1910 technical (97.5% pure) to male and female Charles River rats at dose levels of 32, 16 and 8 mg/kg/day for 13 weeks was without observable adverse effect. The high dose (32 mg/kg/day) was identified as the No-Observed-Adverse-Effect Level (NOAEL) for this study (Woodard Research Corp., 1967b).

- Dietary feeding of Sutan® Technical and Sutan® Analytical (purities not specified) to male Sprague-Dawley rats at dose levels as high as 180 mg/kg/day for 15 weeks was without observable adverse effect (NOAEL) (Scholler, 1976).

- Results of a toxicity study in which male and female beagle dogs were fed R-1910 Technical (97.6% pure) at dietary levels of 450, 900 and 1,800 ppm (corresponding to doses of 11, 23 and 45 mg/kg/day, assuming 1 ppm equals 0.025 mg/kg/day from Lehman, 1959) for 16 weeks were unremarkable (Woodard Research Corp., 1967c). Hence, 45 mg/kg/day is identified as a NOAEL.

- Sutan® Technical (98% pure) was fed in the diet to male and female Sprague-Dawley rats at dose levels of 10, 30 and 90 mg/kg/day for 56 weeks. One group of rats was given 90 mg/kg/day for 15 weeks followed by 180 mg/kg/day for 41 weeks. No systemic effects were found at 10 mg/kg/day. Testes/body weight ratios were significantly ($p < 0.05$) lower in terminally sacrificed males given 30 and 90 mg/kg/day. Slight (8 to 15%) nonsignificant ($p > 0.05$) mean body weight decreases were found in 30 and 90 mg/kg males and 90 mg/kg females. Liver to body weight increases and testicular lesions were found with the highest doses. Blood clotting parameters were affected at all doses, with the effects at 10 mg/kg/day being significant ($p < 0.05$) decreases in factor II times in males and activated partial thromboplastin times in females. The 10 mg/kg/day dose is considered a NOAEL as explained on page 9 of this document (Hazelton Laboratories, Inc., 1978).

- R-1910 Technical (purity not specified) was fed in the diet to male and female Sprague-Dawley CD rats at dose levels of 50, 100, 200 and 400 mg/kg/day for 2 years. Although significantly ($p < 0.05$) elevated liver-to-body weight ratios occurred in terminally sacrificed males given 50 mg/kg/day, this effect was not observed in animals from this dose group sacrificed at 12 and 18 months. Hence, 50 mg/kg/day was identified as a NOAEL. In males and females, body weights were significantly ($p < 0.05$) reduced, and liver to body weight ratios were significantly ($p < 0.05$) increased with doses above 50 mg/kg/day. Neoplastic nodules and periportal hypertrophy in the liver were significantly ($p < 0.05$) increased in males given 400 mg/kg/day (Biodynamics, 1982).

- Male and female Charles River CD-1 mice were given Sutan® Technical (98% pure) in the diet at dose levels of 20, 80 and 120 mg/kg/day for 2 years. No effects were found at 20 mg/kg/day (NOAEL). Kidney and liver lesions were noted with higher doses (International Research and Development Corporation [IRDC], 1979).

Reproductive Effects

- Twenty five male and 25 female CrlCD(SD)BR rats were fed diets containing 0, 200, 1,000, or 4,000 ppm (0, 10, 50, or 200 mg/kg/day) Sutan® Technical (98.2% pure) for 63 days before the animals were mated (P0 group). Two matings were done to produce the F1a and F1b litters of the first generation. Parental rats obtained from the first generation (P1 group) were mated three times to produce the F2a, F2b, and F2c litters of the second generation. Assessments included survival, body and organ weights, reproductive success, and pathology. Significant ($P < 0.05$) effects at 50 mg/kg/day were increased liver:body weight ratios in P0 females, decreases in body weights of P1 females and food consumption by P0 males, decreased body weights in F2a pups, and decreased brain weights in F1b male weanlings. At 200 mg/kg/day, increased ($P < 0.05$) incidences of dilated renal pelvis and retinal folds in F1b rats were evident. The NOAEL is 10 mg/kg/day.

Developmental Effects

- Sutan® Technical (98.2% pure) was administered by gavage to pregnant rats at doses of 40, 400 and 1,000 mg/kg/day on days 6 through 20 of gestation. The 40 mg/kg/day dose was without observable effect (NOAEL). Higher doses decreased body weight gain in dams, increased liver-to-body weights in dams, decreased fetal body weights, increased incidences of misaligned sternebrae and delayed ossification, and increased early resorptions. Sutan® was not teratogenic in this study (Stauffer Chemical Co., 1983).

- Administration of R-1910 Technical (97.6% pure) in the diet to pregnant Charles River mice at dose levels of 4, 8 and 24 mg/kg/day either on days 6 through 18 or from day 6 until natural delivery was without observable effect (NOAEL) on dams and fetuses (Woodard Research Corp., 1967d).

Mutagenicity

- Butylate was not mutagenic in *Salmonella typhimurium* strains TA1535, TA1537, TA1538 and TA100 with or without the S-9 activating fraction (Eisenbeis et al., 1981).

- In *Drosophila melanogaster*, butylate treatment increased the frequency of sex-linked recessive lethals but had no effect on the frequency of dominant lethals (Murnik, 1976).

Carcinogenicity

- R-1910 Technical was not determined to be carcinogenic in the 2-year rat study by Biodynamics (1982), but a significant ($p < 0.05$) increase in neoplastic nodules in liver in high-dose males was evident. Neoplastic nodules were found in 2/69, 6/69, 1/69, 1/70 and 9/70 males given 0 ppm (control), 50 ppm, 100 ppm, 200 ppm and 400 ppm, respectively. Hepatocellular carcinomas were found in 2/69, 3/69, 4/69, 3/70 and 2/70 males given 0 ppm (control), 50 ppm, 100 ppm, 200 ppm and 400 ppm, respectively.

- Sutan® Technical was not carcinogenic in the 2-year mouse study by IRDC (1979).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL\ or\ LOAEL) \times (BW)}{(UF) \times (\_\_\_\ L/day)} = \_\_\_\ mg/L\ (\_\_\_\ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for butylate. It is, therefore, recommended that the Ten-day HA value (2 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The teratology study in mice by Woodard Research Corporation (1967d) has been selected to serve as the basis for determination of the Ten-day HA value for butylate because it provides a short-term NOAEL (24 mg/kg/day for 13 days) for both maternal and fetal toxicity. The teratology study in rats by Stauffer (1983), which identified a NOAEL of 40 mg/kg/day (for 15 days) for maternal and fetal effects, could also be considered; however, because doses higher than the 24 mg/kg/day NOAEL were not included in the Woodard study (1967d), the effect levels in this study are uncertain. Furthermore, the agent was given in the diet in the Woodard study (1967d) and by gavage in the Stauffer (1983) study. Therefore, dose-response comparisons in terms of both effect and no-effect levels between the Woodard (1967d) and Stauffer (1983) studies cannot be made.

Using a NOAEL of 24 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-Day HA} = \frac{(24\ \text{mg/kg/day})\ (10\ \text{kg})}{(1\ \text{L/day})\ (100)} = 2.4\ \text{mg/L}\ (2{,}000\ \text{ug/L})$$

where:

24 mg/kg/day = NOAEL based on the absence of fetal and maternal effects in mice exposed to Sutan® Technical orally for 13 days.

10 kg = assumed body weight of a child.

1 L/day = assumed daily water consumption of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Longer-term Health Advisory

The DWEL adjusted for a 10 kg child (1 mg/L) is recommended for use as a conservative estimate of the Longer-term HA by the rationale given below.

The 56-week feeding study with Sutan® Technical in rats by Hazelton Laboratories (1978) is a possible basis for a Longer-term HA. However, effects observed in this study were not evident with higher doses in the 2-year feeding study with R-1910 Technical in rats by Biodynamics, Inc. (1982). Effects on blood clotting parameters (decrease in factor II times in males and activated partial thromboplastin times in females) at the 10 mg/kg/day dose and higher in the Hazelton (1978) study are considered to be of questionable toxicological significance because it is not certain whether they actually represent adverse effects, and these effects were not found in the 2-year rat study by Biodynamics (1982).

The 16-week and 13-week feeding studies with R-1910 Technical in dogs and rats, respectively, by Woodard Research Corp. (1967b,c) can also be proposed for calculation of the Longer-term HA. However, the highest estimated dose of 45 mg/kg/day was the NOAEL in the dog study, and the highest dose of 32 mg/kg/day was the NOAEL in the rat study. Each generation in the 2-generation in rats by Stauffer (1986) can, in effect, also be considered an assessment of subchronic toxicity. Because this study does provide a NOAEL (10 mg/kg/day) and a LOAEL (50 mg/kg/day), it is preferred over the studies by Woodard et al. (1967b,c) in which the data suggest that higher doses in these studies could have been NOAELs approximating the dose that is a LOAEL in the Stauffer (1986) study.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose

(RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-generation study with Sutan in rats by Stauffer (1986) is selected to serve as the basis for the Lifetime HA value for butylate. Of the available data, this study is considered to represent the most sensitive endpoint of toxicity in terms of the lowest NOAEL.

The Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(10\ \text{mg/kg/day})}{(100)} = 0.1\ \text{mg/kg/day}\ (100\ \text{ug/kg/day})$$

where:

10 mg/kg/day = NOAEL, based on the absence of toxic signs in a 2-generation study in rats.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.*

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.1\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 3.5\ \text{mg/L}\ (4{,}000\ \text{ug/L})$$

where:

0.1 mg/kg/day = RfD.

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* The data base is adequate to support an uncertainty factor of 100. Stauffer Chemical Company has also submitted a chronic toxicity study in dogs and a developmental effects study in rabbits, but they have not yet been reviewed by the EPA Office of Pesticide Programs.

70 kg = assumed body weight of adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (3.5\ \text{mg/L})(20\%) = 0.7\ \text{mg/L}\ (700\ \text{ug/L})$$

where:

3.5 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Available toxicity data do not determine butylate to be carcinogenic. Although a significant ($p < 0.05$) increase in neoplastic nodules in the liver of male rats fed the highest dose compared to concurrent controls in the 2-year study by Biodynamics (1982) was found, concurrent control incidence (2.89%) was low compared to laboratory historical control data (average of 7.07%).
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), butylate may be placed in Group D: not classified. This category is for substances that show inadequate evidence of carcinogenicity in animals and humans.
- The U.S. EPA has not calculated excess lifetime cancer risks for this material.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Residue tolerances for butylate have been established by the U.S. EPA (1985) and include 0.1 ppm in or on corn grain, fresh corn, corn forage and fodder, sweet corn and popcorn. A tolerance is a derived value based on residue levels, toxicity data, food consumption levels, hazard evaluation and scientific judgment, and it is the legal maximum concentration of a pesticide in or on a raw agricultural commodity or other human or animal food (Paynter et al., undated).
- The U.S. EPA Office of Pesticide Programs has calculated a provisional ADI of 70 ug/kg/day, based on the 20-mg/kg/day NOAEL in the 2-year mouse study by IRDC (1979) and a 300-fold uncertainty factor (used because of data gaps, including a chronic feeding study in dogs, a reproduction study in rats and a teratology study in rabbits, in the total data package).

VII. ANALYTICAL METHODS

- Analysis of butylate is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus-containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen-phosphorus detector. The method detection limit has not been determined for butylate, but it is estimated that the detection limits for analytes included in this method are in the range of 0.1 to 2 ug/L. This method has been validated in a single laboratory end estimated detection limits have been determined for the analytes, including butylate. The estimated detection limit is 0.15 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information was found in the available literature on treatment technologies capable of effectively removing butylate from contaminated water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

CARBARYL

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

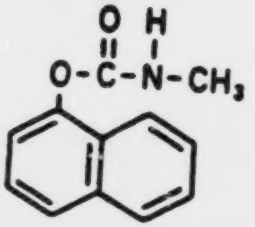
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 63-25-2

Chemical Structure



1-Naphthalenol methylcarbamate

Synonyms

- Arilate; Bercema NMC50; Caprolin; Sevin; Vioxan (Meister, 1983).

Uses

- Contact insecticide used for the control of pests on more than 100 different crops, forests, lawns, ornamentals, shade trees and rangeland (Meister, 1983).

Properties (Windholz et al., 1983; CHEMLAB, 1985)

Chemical Formula	$C_{12}H_{11}O_2N$
Molecular Weight	201.22
Physical State (25°C)	White crystals
Boiling Point	--
Melting Point	145°C
Density	1.232 (20°C)
Vapor Pressure (25°C)	$<4 \times 10^{-5}$ mm Hg
Water Solubility (30°C)	120 mg/L
Log Octanol/Water Partition Coefficient	0.14
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Carbaryl has been found in 58 of 640 surface water samples analyzed and in none of 1,541 ground water samples (STORET, 1988). Samples were collected at 185 surface water locations and 1,409 ground water locations, and Carbaryl was found in 6 states. The 85th percentile of all nonzero samples was 260 ug/L in surface water and 0 ug/L in ground water sources. The maximum concentration found was 180,000 ug/L in surface water and 0 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity.

of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- ^{14}C-Carbaryl (purity unspecified) at 10 ppm was relatively stable to hydrolysis in buffered solutions at pH 3 and 6. It hydrolyzed at pH 9 with a half-life of 3 to 5 hours when incubated at 25°C (Khasawinah and Holsing, 1977a). At 35°C, ^{14}C-carbaryl was stable at pH 3, and hydrolyzed with a half-life of >28 days and 30 to 60 minutes at pH 6 and 9, respectively. 1-Naphthol was the major degradate formed.

- ^{14}C-Carbaryl (purity unspecified) at 5 ppm photodegraded slowly in 0.1 M phosphate buffer solutions, with 4.39 to 4.49 ppm remaining as parent compound after 18 days of irradiation (Khasawinah and Holsing, 1977b). In a 2% acetone solution, ^{14}C-carbaryl accounted for 3.63 to 3.65 ppm after 18 days. 1-Naphthol and several unidentified compounds were found at <0.07 ppm.

- Under aerobic conditions, ^{14}C-carbaryl (>99% pure) at 1 ppm degraded with a half-life of 7 to 14 days in a sandy loam soil maintained at 15 or 23 to 25°C, and 14 to 28 days in a clay loam soil maintained at 23 to 25°C (Khasawinah and Holsing, 1978). Degradation was slightly slower in sterile soils (half-lives of 14 to 56 days). The majority of the applied radioactivity was bound to the soil or had been evolved as $^{14}CO_2$ by the end of the test period (112 days). No degradates were found.

- Under aerobic conditions, ^{14}C-carbaryl (>99% pure) at 1 ppm degraded with a half-life of 84 to 112 days in a flooded sandy loam soil (Khasawinah and Holsing, 1978). At 168 days after treatment, ^{14}C-carbaryl accounted for 42% of the applied radioactivity in the soil and water layer. 4-Hydroxy carbaryl was found at <0.3% of the applied radioactivity in soil samples taken after 112 days. Approximately 20% of the total radioactivity was soil-bound at 112 days.

III. PHARMACOKINETICS

Absorption

- Comer et al. (1975) reported the results of tests conducted in factory workers exposed to carbaryl during the formulation of 4 and 5% carbaryl dust. Carbaryl exposure via the skin was measured by attachment of a special gauze pad to various parts of the body, and inhaled carbaryl was measured by the use of special filter pads in face masks. Calculated exposures were 73.90 and 1.10 mg/hour for the dermal and respiratory routes, respectively. The total exposure was 75 mg/hour, or 600 mg/day. Absorption levels were determined by estimation of the carbaryl metabolite 1-naphthol in urine. It was determined that during an 8-hour workday the total absorption of carbaryl would be 5.6 mg. This is about 0.9% of the total exposure, and the authors interpreted this to mean that dermal absorption was not complete.

- Feldmann and Maibach (1974) applied 4 ug/cm^2 of ^{14}C-labeled carbaryl (position of label not specified) dissolved in acetone to one or both forearms of apparently healthy male volunteers. The area of application was left unwashed and unprotected for 24 hours. Based on the excretion rate, it was determined that 73.9% of the applied carbaryl was absorbed through the skin.

- Houston et al. (1974) reported that ^{14}C-carbamyl-labeled carbaryl administered by gavage to male rats at doses of 0.5 mg/kg (given as 0.5 mL of 0.5% propylene glycol in water) rapidly appeared in the systemic circulation. Within a few minutes, the plasma level was 50 ng/mL. A maximum level of 150 ng/mL was reached in less than 10 minutes and steadily declined to 20 ng/mL at 120 minutes. Only 4.6% of the dose was excreted in the feces, indicating that at least 95.3% had been absorbed.

- Falzon et al. (1983) administered single doses of 20 mg/kg of ^{14}C-carbaryl (in olive oil) to six female rats by gavage. After 24 hours, 5.8% of the label was recovered in the feces, indicating that about 94.2% had been absorbed.

Distribution

- The distribution of ^{14}C-carbonyl-labeled carbaryl in male and female rats after administration of 1.5 mg/kg by stomach tube was examined in eight body tissues (Krishna and Casida, 1965). The amounts detected (umol/kg) in males and females, respectively, were: cecum, 0.17 and 0.60; esophagus, 0.05 and 0.05; large intestine, 0.20 and 0.30; small intestine, 0.06 and 0.08; kidney, 0.06 and 0.07; liver, 0.11 and 0.112; spleen, 0.05 and 0.08; and stomach, 0.07 and 0.14.

- Falzon et al. (1983) administered single oral doses of 20 mg/kg of ^{14}C-carbaryl to female Wistar rats by gavage. The amounts detected 24 hours after administration were 0.11% in the brain, 3.87% in the digestive tract and 13.31% in the carcass.

Metabolism

- Human tissues obtained by either biopsy or autopsy were incubated using an in vitro organ-maintenance technique with ^{14}C-(N-methyl)-labeled carbaryl (Chin et al., 1974). The following tissues were examined: for males -- lung, liver and kidney; for females -- liver, placenta, vaginal mucosa, uterus and uterine tumor (leiomyoma). Hepatic tissues metabolized carbaryl by hydrolysis and/or demethylation, hydroxylation and oxidation followed by conjugation. The primary hydrolytic product was 1-naphthol (42% by 24 hours at pH 7.8). The kidney produced naphthyl glucuronide; the uterus, lung and placenta produced naphthyl sulfate from carbaryl. The vaginal mucosa produced glucuronide and sulfate conjugates, but only a slight amount of conjugating activity (naphthol sulfate) was found in the uterine leiomyoma.

- Houston et al. (1974) administered ^{14}C-carbamyl-labeled carbaryl (0.5 mg/kg) to male rats by gavage. Within 48 hours, 54.5% of the label had been excreted in the urine as metabolites (not identified). In addition, 32.9% was excreted as CO_2. This indicated that carbaryl was extensively metabolized in rats.

Excretion

- Comer et al. (1975) studied the excretion of 1-naphthol in the urine of workers who were exposed to carbaryl in a pesticide formulation plant. The workers were exposed to carbaryl both dermally (73.9 mg/hour) and by inhalation (1.1 mg/hour). Analyses of urine samples indicated that the excretion rate of 1-naphthol varied from 0.004 to 3.4 mg/hour, with a mean value of 0.5 mg/hour. This corresponds to an excretion rate of 0.7 mg carbaryl/hour. Following exposure to carbaryl at the start of the workday, the urinary level of 1-naphthol increased, reached its maximum level during the late afternoon and evening hours, and then dropped to a lower level before the start of the next day's workday.

- Urinary excretion of topically applied radiolabeled carbaryl in healthy male volunteers was measured by Feldman and Maibach (1974). A total of 26.1% of the dose was recovered in the urine over a 5-day period.

- Krishna and Casida (1965) administered single doses of 1.5 mg/kg of ^{14}C-carbonyl-labeled carbaryl orally to rats. Excretion of the label for male and female animals, respectively, was as follows: expired carbon dioxide, 26% and 26%; urine, 64.0% and 72.0%; and feces, 4.0% and 4.0%.

- Houston et al. (1974) administered ^{14}C-carbamyl-labeled carbaryl (0.5 mg/kg) by gavage to male rats. The label was almost completely excreted within 48 hours, with the following distribution: expired carbon dioxide- 32.9%; urine, 54.5%; and feces, 4.6%. Less than 1% of the label in urine was unchanged carbaryl. About 6.0% of the label remained in the body. Biliary excretion was examined by bile-duct cannulation. Within 6 hours, 30 to 33% of the administered dose was present in the bile; after 6 hours, the amount in the bile leveled off.

IV. HEALTH EFFECTS

Humans

- Vandekar (1965) investigated the effects of large-scale carbaryl spraying in a village in Nigeria. No quantitative estimates of exposure were obtained, but plasma cholinesterase (ChE) activity was decreased by about 15% in eight applicators (spraymen) and by an average of 8% in 63 villagers.

- Wills et al. (1968) studied the subchronic toxicity of carbaryl in human volunteers. Groups of five or six men were given daily oral doses of 0, 0.06 or 0.13 mg/kg/day for 6 weeks. At the lower dose, no significant effects were detected on kidney function, electroencephalogram, hematology, blood chemistry, urinalysis or plasma and red blood cell ChE activity. At the higher dose, the only detectable effect was a slight increase in the urinary ratio of amino acid nitrogen to creatinine. This was interpreted to suggest a slight decrease in resorption of amino acids in the kidney. This effect was fully reversible. Based on these observations, a No-Observed-Adverse Effect Level (NOAEL) of 0.06 mg/kg/day was identified.

Animals

Short-term Exposure

- Carpenter et al. (1961) investigated the acute oral toxicity of carbaryl in several species. Cats were found to be most sensitive (2/2 deaths at 250 mg/kg). Guinea pigs, rats and rabbits were less sensitive, with calculated LD_{50} values of 280, 510 and 710 mg/kg, respectively. No deaths were reported in dogs administered doses up to 795 mg/kg/day.

- The acute oral toxicity of carbaryl in male Sprague-Dawley rats was studied by Rittenhouse et al. (1972). Carbaryl (99.9% active) dissolved in acetone and propylene glycol (10% v/v) was administered in a single dose at four dose levels to six animals per level. Animals were observed for 14 days following treatment. Dose levels were 439, 658, 986 or 1,481 mg/kg. Mortalities observed at these levels were 0/6, 0/6, 4/6 and 5/6 rats, respectively. Most deaths occurred in the first 24 hours. The LD_{50} was calculated to be 988 mg/kg. Animals at all dose levels exhibited symptoms of ChE inhibition, but ChE activity was not measured. No other parameters were reported.

- Carpenter et al. (1961) fed single oral doses of carbaryl in capsules to female mongrel dogs as follows: 250 mg/kg (one animal), 375 mg/kg (four animals) or 500 mg/kg (one animal). Signs of overstimulation of the parasympathetic nervous system were observed at the two higher doses, but not at 250 mg/kg. These signs included: increased respiration, lacrimation, salivation, urination, defecation, muscular twitching, constriction of pupils, poor coordination and vomiting. Plasma ChE was not affected at 375 mg/kg, but a transient decrease (24 to 33%) was observed in erythrocyte ChE at this dose. After 1 day, the appearance of the animals was normal and no adverse CNS effects were noted. Based on the absence of visible external effects or inhibition of ChE, this study identified a NOAEL of 250 mg/kg.

- Carpenter et al. (1961) also administered single oral doses of carbaryl (560 mg/kg, by gavage in corn oil) to three groups of rats (seven to nine per group). Groups were sacrificed after 0.5, 4 or 24 hours, and ChE activity was measured in plasma, erythrocytes and brain. Plasma ChE was slightly lower (7 to 14%) than control, but this was not statistically significant. In erythrocytes, ChE was inhibited 42% after 0.5 hours, but this returned to near normal (86% of control) within 24 hours. Brain ChE activity was inhibited 30% after 0.5 hours, and this returned toward normal (91% of control) by 24 hours.

- Weil et al. (1968) fed carbaryl in the diet for 1 week to Harlan-Wistar albino rats (42-days old) at concentrations yielding ingested doses of 0, 10, 50, 250 or 500 mg/kg/day. Body weight gain was decreased in animals exposed to 50 mg/kg/day or higher. At 10 mg/kg/day, ChE activity was not significantly affected in plasma, red blood cells or brain. At 50 mg/kg/day, plasma ChE was decreased 15 and 18% and red blood cell ChE was decreased 26 and 47% in females and males, respectively. At higher doses, larger decreases in plasma and red blood cell ChE were seen, brain ChE was also decreased (26 and 23% at 250 mg/kg/day and 28 and 33% at 500 mg/kg/day in males and females, respectively). After 1 day on control diet, these effects on ChE were entirely reversed. Based on these data, a NOAEL of 10 mg/kg/day and a Lowest-Observed-Adverse Effect Level (LOAEL) of 50 mg/kg/day were identified in rats.

Dermal/Ocular Exposure

- Carpenter et al. (1961) applied 0.01 mL of 10% carbaryl in acetone (a dose of 1 mg) to the clipped skin of the belly of five rabbits. No irritation was detected.

- Gaines (1960) applied a series of doses of carbaryl dissolved in xylene to the skin of Sherman rats. The dermal LD_{50} value was greater than 4,000 mg/kg for both males and females.

- Carpenter et al. (1961) detected a weak skin sensitization reaction in 4 of 16 male albino guinea pigs given eight intracutaneous injections of 0.1 mL of 0.1% carbaryl (0.1 mg/dose). The challenge dose (not specified) was given 3 weeks later, and examinations for sensitization reaction were performed 24 and 48 hours thereafter.

- Carpenter et al. (1961) applied carbaryl to the eyes of rabbits and evaluated corneal injury. Technical carbaryl (98% pure) applied as a 10% suspension in propylene glycol caused mild injury in 1/5 eyes. A 25% aqueous suspension caused no injury, and 50 mg of powder caused only traces of corneal necrosis.

Long-term Exposure

- Wistar rats (five/sex, 45-days old) were fed carbaryl (as Compound 7744; purity not specified) in the diet for 90 days at levels of 0.0037, 0.011, 0.033 or 0.10% (Weil, 1956). Assuming that 1 ppm in the diet of young rats is equivalent to approximately 0.10 mg/kg/day (Lehman, 1959), this corresponds to doses of about 3.7, 11, 33 or 100 mg/kg/day. The author stated that there were no significant changes in appetite or weight gain when compared to the controls; micropathology revealed no changes in lung, liver or kidney tissue at any dose level. It was concluded that for these end points the effect level for toxicity is higher than 0.10%, which is equivalent to a NOAEL of about 100 mg/kg/day (the highest dose tested).

- Carbaryl was administered to male rats by gavage at a level of 200 mg/kg, 3 days a week for 90 days (Dikshith et al., 1976). This corresponds to an average dose of 86 mg/kg/day. The control animals received vehicle (peanut oil) on a similar schedule. There were no overt toxicological signs in these rats, and no marked biological changes were seen in testes, liver and brain (enzymatic determinations) except for ChE activity, which was inhibited 34% in blood ($p < 0.001$) and 12% in brain ($p < 0.05$). No significant histological changes were noted in testes, epididymis, liver or kidney. Based on ChE inhibition, the LOAEL for this study was identified as 86 mg/kg/day.

- Carpenter et al. (1961) fed carbaryl to male and female Basenji-Cocker dogs (four or five per dose) for 1 year. Dietary levels were about 0, 24, 95 or 414 ppm, which were adjusted to supply ingested doses of 0, 0.45, 1.8 or 7.2 mg/kg/day. No compound-related effects were detected on mortality, body weight, hematocrit, hemoglobin, leukocyte count, blood chemistry, plasma or erythrocyte ChE activity, or liver and kidney weights. Microscopic examination of tissues revealed diffuse cloudy swelling of renal nephrons and focal debris in glomeruli of dogs fed the higher dose. These conditions were also observed in controls, but less frequently, and the authors judged they were not early stages of toxic degeneration. One dog at the low dose displayed a transient hind leg weakness after 189 days. This disappeared within 3 weeks, although dosing was continued throughout. Subsequent microscopic examination revealed no differences between this dog and others. A NOAEL of 7.2 mg/kg/day (the highest dose tested) was identified.

- Schering (1963) administered carbaryl (5.0 mg/kg/day) by gavage to 25 male and 25 female rats, 5 days per week for 18 months. No effects were observed on weight gain, organ weights, urinalysis, hematology or histologic appearance of tissues. The authors concluded that 5.0 mg/kg/day was a NOAEL in rats.

- Carpenter et al. (1961) studied the toxicity of carbaryl in a 2-year feeding study in rats. Groups of 20 male and 20 female CF-N rats (60-days old) were maintained on a diet containing 0, 50, 100, 200 or 400 ppm dry Sevin. Based on measured food consumption and body weights, the authors reported the doses to be equivalent to 0, 2.0, 4.0, 7.9 or 15.6 mg/kg/day in males, and 0, 2.4, 4.6, 9.6 or 19.8 mg/kg/day in females. No adverse effects were detected on life span, food consumption, body weight gain, liver and kidney weights, cataract formation or hematocrit. Histological examination after 1 year revealed mild changes in the kidney, characterized by cloudy swelling of the nephrons. This was statistically significant ($p < 0.004$) at the high dose. Cloudy swelling of hepatic chords was also observed at the high dose, and this was significant after 2 years ($p < 0.002$). No histological changes were detectable at the lower doses. Based on these observations, a NOAEL of 7.9 mg/kg/day for males and 9.6 mg/kg/day for females was identified.

Reproductive Effects

- Weil et al. (1972a) investigated the reproductive effects of carbaryl in female rats exposed either by gavage or by feeding. Doses of 0, 2.5 and 10 mg/kg/day ingested from the diet for three generations resulted in no statistically significant, dose-related effects on fertility, gestation, lactation or pup viability. Doses of 100 mg/kg/day given by gavage (5 days/week, beginning at 5 weeks of age) resulted in maternal mortality, reduced fertility and signs of ChE inhibition. These signs were not seen in animals ingesting doses of up to 200 mg/kg/day from the diet.

- Murray et al. (1979) studied the reproductive effects of carbaryl (99% active ingredient) in female CF-1 mice. Carbaryl was administered by gavage at 100 or 150 mg/kg/day, or by feeding in the diet at 5,660 ppm (calculated by the authors to be equivalent to 1,166 mg/kg/day). At the gavage dose of 150 mg/kg/day, the mice gained less weight and exhibited significant maternal toxicity, including salivation, ataxia and lethargy, and 10/37 females died during the experimental period. At 100 mg/kg/day by gavage, a single maternal death occurred, but weight gain was normal and no other evidence of maternal toxicity was observed. No maternal deaths or signs of ChE inhibition were seen among the mice supplied carbaryl in the diet (1,166 mg/kg/day), although there was a significant ($p < 0.05$) decrease in body weight gain on days 10 through 15. The incidence of pregnancy, the average number of live fetuses/litter and the incidence of resorptions were not altered by carbaryl for either route of administration. Mean fetal body weight and length were significantly ($p < 0.05$) lower than control values among litters given carbaryl in the diet, but was not affected among those given carbaryl by gavage. Based on maternal reproductive effects, the NOAEL in mice was identified as 100 mg/kg/day.

- In an investigation using Sprague-Dawley rats, carbaryl was administered by gavage at levels of 1, 10 or 100 mg/kg/day for 3 months prior to and throughout gestation (Lechner and Abdel-Rahman, 1984). Carbaryl of formulation grade (purity not specified) was administered in corn oil. Dams were sacrificed on day 20 for examination. Animals receiving 100 mg/kg/day showed a significant decrease in weight gain during the gestational period, occurring primarily in the third week (days 15 to 20). There was also a slight decrease in the number of implantation sites and live fetuses per dam after treatment at this dose level. Fetal weights and body length for all three doses were within the range of control values. There were no overt signs of maternal toxicity that suggested ChE inhibition. Based on maternal weight gain and number of implantations, the NOAEL in this study was identified as 10 mg/kg/day.

- Collins et al. (1971) reported the effects of carbaryl in the diet on various reproductive parameters over three generations of rats. Osborne-Mendel rats were fed 0, 2,000, 5,000 or 10,000 ppm carbaryl in the diet. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0, 100, 250 or 500 mg/kg/day. At 10,000 ppm, no litters were produced after the first litter of the second generation; decreases were observed in the fertility, viability, survival and lactation indices in all litters at this dose. The survival index also showed a decrease at the 5,000-ppm level. Dose-related decreases were observed in the ratio of average number of animals weaned per number of litters at both 5,000 and 10,000 ppm. At all three dose levels there was a decrease in weanling weights. In rats, the LOAEL was identified as 2,000 ppm (100 mg/kg/day).

- Collins et al. (1971) reported the effects of carbaryl in a three-generation study in gerbils. Carbaryl was fed at dose levels of 0, 2,000, 4,000, 6,000 or 10,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), and that gerbils are similar to rats in terms of body weight and food consumption, this corresponds to doses of about 0, 100, 200, 300 or 500 mg/kg/day. No second litters were produced in the third generation at 10,000 ppm. Decreases in the viability index were observed at 6,000 and 10,000 ppm. Dose-related decreases in the survival index were also observed. The average number of animals weaned per litter was also decreased. Based on these findings, a LOAEL of 6,000 ppm (300 mg/kg/day) and a NOAEL of 4,000 ppm (200 mg/kg/day) were identified.

Developmental Effects

- Weil et al. (1971) exposed pregnant Harlan-Wistar rats to carbaryl in the diet on days 5 to 15 of gestation. Ingested doses were 0, 20, 100 or 500 mg/kg/day. Animals were sacrificed on days 19 to 21, and fetuses were examined for soft-tissue and skeletal abnormalities. No increased incidence of teratogenic anomalies was detected at any dose level. Based on this information, a NOAEL of 500 mg/kg/day (the highest dose tested) was identified.

- Murray et al. (1979) administered 200 mg/kg/day carbaryl to female rabbits by gavage on days 6 to 18 of gestation. Fetuses were removed and examined for developmental defects. There was a significantly ($p < 0.05$) higher incidence of omphalocele in fetuses from exposed animals than in the controls. The anomalies occurred in litters from does that showed the greatest weight losses during the experimental period. No other anomalies were seen at this dose level. At 150 mg/kg/day, there were single cases of omphalocele, hemivertebrae and conjoined nostrils with missing nasal septum, but no fetal alterations occurred at an incidence significantly different from that of the control group. Based on fetal defects, the LOAEL for the rabbit was identified as 150 mg/kg/day.

- Golbs et al. (1975) orally administered carbaryl to Wistar rats at doses of 200 or 350 mg/kg on days 5, 7 and 9, or on days 11, 13 and 15 of the gestation period. In one group of rats, 200 mg/kg was administered on days 5, 7, 9, 11, 13 and 15. Doses of 350 mg/kg given during late gestation (days 11 to 15) delayed fetal development, whereas the same dose given at the earlier interval (days 5 to 9) resulted in loss of fertilized ova and more pronounced retardation in development of individual fetuses. Similar results were produced by the 200-mg/kg dose given on alternate days from day 5 through day 15. It was concluded that carbaryl produces dose-dependent effects on intrauterine development in rats. Based on this study, a LOAEL of 200 mg/kg (100 mg/kg/day) was identified.

- Murray et al. (1979) studied the teratogenic effects of carbaryl in CF-1 mice. Carbaryl was administered by gavage at 100 or 150 mg/kg/day, or by feeding in the diet at 5,660 ppm (calculated by the authors to be equivalent to 1,166 mg/kg/day). No major malformations were detected among the offspring of dams given carbaryl by either route at incidences significantly different than concurrent or historical controls. Delayed ossification of skull bones and of sternebrae occurred significantly more often among litters from dams given carbaryl in the diet, but not in litters from gavage-administered dams. Based on developmental observations in fetuses, the NOAEL in this study was identified as 150 mg/kg/day.

- Lechner and Abdel-Rahman (1984) administered carbaryl to Sprague-Dawley rats by gavage for 3 months prior to and throughout gestation at doses of 0, 1, 10 or 100 mg/kg/day. Dams were sacrificed on day 20, and fetuses were examined for external, skeletal and visceral malformations. There were no statistically significant increases of serious anomalies at any dose level. The authors concluded that in the rats tested, carbaryl displayed no evidence of teratogenicity. On this basis, a NOAEL of 100 mg/kg/day (the highest dose tested) was identified.

- Benson et al. (1967) fed mice carbaryl in their diet (intake levels of 10 or 30 mg/kg/day) on day 6 through termination of gestation. Some dams were allowed to deliver naturally, and others were delivered by Cesarean section. There were no differences between the offspring of the two treated groups and the controls in sex ratio, incidence of anomalies or in ossification. Based on this information, a NOAEL of 30 mg/kg/day (the highest dose tested) was identified.

Mutagenicity

- The effects of pesticides on scheduled and unscheduled DNA synthesis of rat thymocytes and human lymphocytes were studied by Rocchi et al. (1980). Carbaryl (99.2% pure) in the rat thymocyte culture inhibited thymidine uptake 15, 22 and 99% at levels of 1, 10 and 100 ug/mL, respectively. In the human lymphocytes, a dose of 50 ug/mL produced 62% inhibition on scheduled DNA synthesis, but had no effect on unscheduled DNA synthesis.

Carcinogenicity

- Carpenter et al. (1961) fed carbaryl to groups of CF-N rats (20/sex/dose) for 2 years. Concentrations in the diet were 0, 50, 100, 200 or 400 ppm, reported by the authors to be equal to doses of 0, 2.0, 4.0, 7.9 or 15.6 mg/kg/day in males and 0, 2.4, 4.6, 9.6 or 19.8 mg/kg/day in females. Based on gross and histological examination of tissues, no increased frequency of any tumor type was detected. The total number of tumors seen at each of the five concentrations tested was 10, 12, 8, 9 and 12, occurring in 9, 11, 7, 6 and 11 rats, respectively.

- Schering (1963) dosed 25 male and 25 female rats by gavage with 5.0 mg/kg/day carbaryl for 18 months. Based on histological examination of tissues, no effects of carbaryl on tumor frequency were detected.

- Carbaryl (30 mg/kg/day) was administered by gavage to mongrel rats daily for 22 months (Andrianova and Alekseev, 1969). At the termination of the study, 46 of the original 48 controls survived and one animal had a malignant tumor. In the treated rats, 12 of the original 60 survived to 22 months, and 4 of these had malignancies (25%). It was concluded that carbaryl was carcinogenic in this investigation. Statistical analyses of the results were not presented.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were found in the available literature that were suitable for determination of the One-day HA value. It is recommended that the Ten-day HA value for a 10-kg child (1.0 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Weil et al. (1968) has been selected to serve as the basis for determination of the Ten-day HA for the 10-kg child. This study identified a NOAEL of 10 mg/kg/day in rats fed carbaryl in the diet for 7 days, based on inhibition of ChE in plasma and red blood cells.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(10 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)(1 \text{ L/day})} = 1.0 \text{ mg/L } (1{,}000 \text{ ug/L})$$

where:

10 mg/kg/day = NOAEL, based on absence of effects on ChE in rats exposed to carbaryl in the diet for 7 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

No data were found in the available literature that were suitable for the determination of a Longer-term HA value. It is, therefore, recommended that the DWEL, adjusted for a 10-kg child (1.0 mg/L) be used as a conservative estimate of the Longer-term HA value.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in rats by Carpenter et al. (1961) has been selected to serve as the basis for determination of the Lifetime HA for carbaryl. This study identified a NOAEL of 9.6 mg/kg/day, based on absence of effects on mortality, body weight, organ weight, hematology, cataract frequency or histopathology. This value is supported by a 1-year feeding study in dogs, which identified a NOAEL of 7.2 mg/kg/day (Carpenter et al., 1961), and an 18-month oral study in rats, which identified a NOAEL of 5.0 mg/kg/day (Shering, 1963); however, these latter studies were not selected because exposure was less-than-lifetime.

Using the NOAEL of 9.6 mg/kg/day, the Lifetime HA for carbaryl is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(9.6 \text{ mg/kg/day})}{(100)} = 0.1 \text{ mg/kg/day}$$

where:

9.6 mg/kg/day = NOAEL, based on absence of adverse effects in rats fed carbaryl in the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.1 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 3.5 \text{ mg/L } (4{,}000 \text{ ug/L})$$

where:

0.1 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (3.5 \text{ mg/L})\ (20\%) = 0.70 \text{ mg/L } (700 \text{ ug/L})$$

where:

3.5 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- The International Agency for Research on Cancer (IARC) (1976) has classified carbaryl in Group 3; i.e., this chemical cannot be classified as to its carcinogenicity for humans.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), carbaryl may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA/Office of Research and Development determined an Acceptable Daily Intake (ADI) of 0.096 mg/kg/day based on a rat chronic oral NOAEL of 9.6 mg/kg/day (Carpenter, 1961) with an uncertainty factor of 100.
- The National Academy of Sciences (NAS) determined an ADI of 0.082 mg/kg/day based on a rat chronic oral NOAEL of 8.2 mg/kg/day (Union Carbide, 1958) and an uncertainty factor of 100.
- The NAS has also determined a Suggested-No-Adverse-Response-Level (SNARL) of 0.574 mg/L, based on an ADI of 0.082 mg/kg/day (70-kg adult consuming 2 L/day and a 20% source contribution factor) (NAS, 1977).
- The U.S. EPA has established residue tolerances for carbaryl in or on raw agricultural commodities that range from 0.1 to 100 ppm (CFR, 1985).

VII. ANALYTICAL METHODS

- Analysis of carbaryl is by a high performance liquid chromatographic (HPLC) procedure used for the determination of N-methylcarbamoyloximes and N-methylcarbamates in drinking water (U.S. EPA, 1988). In this method the water sample is filtered and a 400 uL aliquot is injected into a reverse phase HPLC column. Separation of compounds is achieved using gradient elution chromatography. After elution from the HPLC column, the compounds are hydrolyzed with sodium hydroxide. The methyl amine formed during hydrolysis is reacted with o-phthalaldehyde (OPA) to form a fluorescent derivative which is detected using a fluorescence detector. The method detection limit has been estimated to be 2.0 ug/L for carbaryl.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) adsorption, ozonation and conventional treatment will remove carbaryl from water. The percentage removal efficiency ranged from 43 to 99%.
- Whittaker (1980) determined adsorption isotherms using GAC on laboratory-prepared carbaryl in water solutions.
- Pilot studies proved that GAC is 99% effective for carbaryl removal (Whittaker et al., 1980 and 1982). Two columns, each packed with 37 kg (80 lbs) of two different GAC, were studied at an empty bed contact time of 8 minutes and an optimum flow rate of 1 gpm.
- Laboratory studies for both batch and flow-through columns were used to examine carbaryl adsorption on two different GAC particle sizes (Whittaker et al., 1982). Data were fitted to both Langmuir and Freundlich isotherms; the monolayer capacity was calculated to be 800 moles carbaryl/gm and 1,250 moles carbaryl/gm for the 1.2 mm and 0.6 mm GAC, respectively.

- Ozonation has been 99% effective in removing carbaryl and its hydrolysis product, naphthol, from aqueous solution (Shevchenko et al., 1982). Carbaryl and naphthol were not detected in the treated effluent after the addition of 24.8 mg/L and 4.8 mg/L, of ozone respectively. Before ozonation can be used to treat carbaryl contaminated drinking water, however, the identity and toxicity of the resulting degradates must be established.

- Conventional water treatment by alum coagulation, 30-minute settling period and filtration removed 56% of the carbaryl present (Whittaker et al., 1982). Alum dosage of 100 mg/L plus the addition of 1 mg/L of anionic polymer achieved this degree of removal of carbaryl from wastewater.

- A 3-day settling period without any chemical treatment yield a 50% carbaryl concentration reduction (Holiday and Hardin, 1981).

- Treatment technologies for the removal of carbaryl from water are available and have been reported to be effective. However, selection of individual or combinations of technologies to attempt carbaryl removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

CARBOXIN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

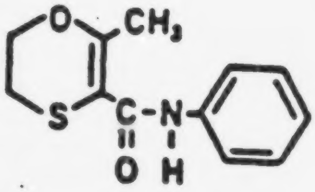
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 5234-68-4

Structural Formula



5,6-Dihydro-2-methyl-N-phenyl-1,4-Oxathiin-3-carboxamide

Synonyms

- Carbathiin; Carboxine; D-735; DCMO; DMOC; F735; Vitavax (Meister, 1983).

Uses

- Systemic fungicide; seed protectant; wood preservative (Meister, 1983).

Properties

(Meister, 1983; Windholz et al., 1983; Wo and Shapiro, 1983; Worthing, 1983; TDB, 1985)

Chemical Formula	$C_{12}H_{13}O_2NS$
Molecular Weight	235.31
Physical State (25°C)	Crystals
Boiling Point	--
Melting Point	93 to 95°C
Density	--
Vapor Pressure (20°C)	<1 mm Hg
Specific Gravity	--
Water Solubility (25°C)	170 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- No information was found in the available literature on the occurrence of carboxin.

Environmental Fate

- Carboxin is rapidly metabolized (oxidized by flavin enzymes found in fungi mitochondria) in aerobic soil. When applied to soil (aerobic conditions), more than 95% of the carboxin was degraded within 7 days. The major degradation product was carboxin sulfoxide, which represented 31 to 54% of the applied radioactivity at 7 days after treatment. Several minor degradation products were also formed (carboxin sulfone, p-hydroxy carboxin and $^{14}CO_2$). Carboxin was degraded in sterile soil but at a much slower rate than in nonsterile soil (46 to 72% degraded in 7 days). This would indicate that soil metabolism of carboxin under aerobic conditions is primarily by microbial processes. Carboxin sulfoxide is stable in anaerobic soil (Chin et al., 1972, 1969, 1970a,b; Dzialo and Lacadie, 1978; Dzialo et al., 1978; Spare, 1979).

- Carboxin sulfoxide, a major metabolite of carboxin, photodegrades to unknown compounds. After 7 days of incubation, 49% of the applied radioactivity was present as unknown compounds (Smilo et al., 1977).

- Carboxin does not readily adsorb to soil [K value (adsorption coefficient) <1] and both carboxin and carboxin sulfoxide are very mobile in soil with about half of the applied radioactivity leaching through 12-inch columns of clay loam soils (Lacadie et al., 1978; Dannals et al., 1976).

- In aqueous solution, carboxin was oxidized to carboxin sulfoxide and carboxin sulfone within 7 days (Chin et al., 1970a).

III. PHARMACOKINETICS

Absorption

- Waring (1973) administered carboxin (Vitavax) by gavage to groups of four to six female New Zealand White rabbits (age not specified; 2.5 to 3 kg) and Wistar rats (age not specified; 200 to 250 g) at 1 mmol/kg (235 mg/kg). In the rats, an average of 40% of the dose was excreted in the feces, mostly as unchanged carboxin. In the rabbits, an average of 10% was recovered in the feces. These data suggest that carboxin is not completely absorbed from the gut, especially in rats.

Distribution

- Waring (1973) administered single oral doses of carboxin (Vitavax, 6.3 uCi/rat) to female Wistar rats (age not specified; 200 to 250 g). Carboxin was labeled either in the heterocyclic or aromatic ring and distribution of label was assessed by autoradiography of whole-body sections. After 2 hours, label was localized in the liver, intestinal tract and salivary gland. After 6 hours, label was also present in the kidney. Only trace levels remained in any tissue after 48 hours. There were no differences in the distribution of the two labeled compounds.

- Nandan and Wagle (1980) fed carboxin to male albino rats (age not specified) for 28 days at dietary levels of 0, 100, 1,000 or 10,000 ppm. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of rats equals approximately 0.05 mg/kg/day. Therefore, these levels correspond to 0, 5, 50 and 500 mg/kg/day. In animals fed the highest dose, maximum levels were detected in the liver (140 ug/g), with lower levels in the kidney (123 ug/g), heart (58 ug/g) and muscle (22 ug/g).

Metabolism

- In the study by Waring (1973), as described previously, female New Zealand White rabbits (age not specified; 2.5 to 3 kg) and Wistar rats (age not specified; 200 to 250 g) were given single oral doses of carboxin by gavage at 1 mmol/kg (235 mg/kg). The principal metabolic pathway was found to be ortho- or parahydroxylation, followed by glucuronidation. In the rats, 32% of the dose was excreted in urine as glucuronides and 7% as unconjugated phenols. In the rabbits, 85% of the dose was excreted in urine as glucuronides and 3% as free phenols. The pattern of phenolic metabolites was the same for carboxin labeled in either the heterocyclic or the aromatic rings, indicating that cleavage of the compound did not occur.

Excretion

- In the study by Waring (1973), as described previously, female New Zealand White rabbits (age not specified; 2.5 to 3 kg) and Wistar rats (age not specified; 200 to 250 g) were given single oral doses of carboxin by gavage at 1 mmol/kg (235 mg/kg). In the rats, 41% was excreted in the feces (largely unchanged carboxin) and 54% was excreted in the urine (15% parent compound, 32% glucuronides, 7% free phenols). In the rabbits, 10% was excreted in the feces and 90% was excreted in the urine (2% parent compound, 85% glucuronides, 3% free phenols).

IV. HEALTH EFFECTS

Humans

- A seven-year-old boy developed headaches and vomiting within 1 hour after ingesting several handfuls of wheat seed treated with carboxin. He was administered ipecac (an emetic) and was asymptomatic 2 hours later. No estimate of the ingested dose was provided (PIMS, 1980).

Animals

Short-term Exposure

- Reagan and Becci (1983) reported that the acute oral LD_{50} for technical carboxin (purity not specified) in young CD-1 mice (age not specified) was 4,150 mg/kg for males and 2,800 mg/kg for females. The average LD_{50} was reported to be 3,550 mg/kg.

- RTECS (1985) reported that the acute oral LD_{50} for carboxin (purity not specified) in the rat (age not specified) was 430 mg/kg.

- Nandan and Wagle (1980) fed carboxin to male albino rats (age not specified) for 28 days at dietary levels of 0, 100, 1,000 or 10,000 ppm. Based on the authors' measurements of food consumption and assuming average body weights of 0.1 kg, these levels corresponded to doses of about 0, 5.5, 59.0 or 311 mg/kg/day. A Lowest-Observed-Adverse-Effect Level (LOAEL) of 100 ppm (5.5 mg/kg/day) was tentatively identified in this study based on fluid accumulation in the liver. However, due to a number of deficiencies in this study, it is not possible to accurately evaluate its validity. These deficiencies include a lack of information on the test animals (e.g., condition at study initiation, numbers used) and the absence of statistical analyses.

Dermal/Ocular Effects

- Holsing (1968a) applied carboxin (D-735; purity and vehicle not specified) to the intact or abraded abdominal skin of rabbits (10/sex/dose; age not specified) at concentrations of 1,500 or 3,000 mg/kg. Five animals of each sex served as controls. Test animals were exposed occlusively for 6 to 8 hours, 5 days per week, for 3 weeks (15 applications). No signs of dermal irritation were observed. The test material stained the skin and precluded readings for erythema.

Long-term Exposure

- Ozer (1966) administered carboxin (D-735; purity not specified) to weanling FDRL (Wistar-derived) rats (10/sex/dose; controls: 15/sex) for 90 days at dietary concentrations of 0, 200, 600, 2,000, 6,000 or 20,000 ppm, intended by the author to correspond to approximate dosage levels of 0, 10, 30, 100, 300 or 1,000 mg/kg/day. All animals survived the 90-day treatment period. Growth, food efficiency, hematology, blood chemistry and urinalysis were reported to be similar in all groups with the exception of increased blood urea nitrogen and decreased hemoglobin at the 12-week interval in females that received 20,000 ppm (1,000 mg/kg/day). No significant dose-related gross pathological changes were observed. Microscopically, a significant number of inflammatory degenerative renal changes were found in animals that received doses of 600 ppm (30 mg/kg/day) or higher. These changes included focal chronic inflammation, protein casts and cortical tubular degeneration. In two animals that received 2,000 ppm (100 mg/kg/day), some fibrosis in the medulla was observed. Based on renal changes, a LOAEL of 600 ppm (30 mg/kg/day) and a No-Observed-Adverse-Effect Level (NOAEL) of 200 ppm (10 mg/kg/day) can be identified.

- Jessup et al. (1982) administered carboxin (technical Vitavax; purity not specified) to six-week old Charles River CD-1 mice (50/sex/dose; controls: 75/sex) for approximately 84 weeks at dietary concentrations of 0, 50, 2,500 or 5,000 ppm. The authors indicated that these dietary levels corresponded to doses of about 0, 8, 385 or 751 mg/kg/day for males and 0, 9, 451 or 912 mg/kg/day for females. No compound-related effects on general behavior or appearance were reported. Survival rates of females receiving 5,000 ppm (912 mg/kg/day) were significantly ($p < 0.01$) lower than controls. No compound-related effects on body weight gain, food consumption, or various hematological parameters were reported. No gross pathologic lesions that were considered to be related to compound administration were observed at necropsy in any mice in any treatment group. Microscopically, compound-related effects on the liver, consisting of hypertrophy of the centrilobular parenchymal cells, were observed in mice in the 2,500- or 5,000-ppm dose groups (385 and 751 mg/kg/day for males; 451 and 912 mg/kg/day for females). No other non-neoplastic lesions that could be attributed to compound administration were observed. The NOAEL in this study is 50 ppm (8 mg/kg/day for males; 9 mg/kg/day for females) based on hepatic effects.

- Holsing (1969a) administered carboxin (technical D-735; considered to be 100% active ingredient) to Charles River rats (30/sex/dose; controls: 60/sex) for 2 years at dietary concentrations of 0, 100, 200 or 600 ppm. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of rats equals approximately 0.05 mg/kg/day. Therefore, these dietary levels correspond to dose levels of approximately 0, 5, 10 or 30 mg/kg/day. While the age of the animals was not specified, the weights of the male rats at initiation ranged from 65 to 88 g and the weight of the female rats ranged from 59 to 85 g. No compound-related effects in terms of physical appearance, behavior, hematology, blood chemistry or urinalysis were reported at any dose level. Observations at terminal necropsy did not reveal any compound-related gross or microscopic changes in the organs of animals at any dose level. At the 600-ppm level (30 mg/kg/day), body weight gain was significantly depressed in both sexes, and food consumption by males was lower than that of controls throughout most of the study (significantly lower during the first 26 weeks). Food consumption by females at all dose levels was generally comparable to controls. Compound-related effects included an increase in mortality at 18 months in males that received 600 ppm (30 mg/kg/day), and changes in absolute and relative organ weights at all dose levels, including increases in thyroid weight and decreases in kidney, heart and spleen weight and histopathological changes in the kidneys at the 12-month interval in both sexes at 200 and 600 ppm. Most of these effects were inconsistent and were not observed at the end of the study period. At the end of the 2-year study, decreased kidney weights were observed in males at 600 ppm (30 mg/kg/day). Therefore, based on the information presented in this study, a NOAEL of 200 ppm (10 mg/kg/day) was identified.

- Holsing (1969b) administered carboxin (technical D-735; considered to be 100% active ingredient) to young adult beagle dogs (4/sex/dose; controls: 6/sex) for 2 years at dietary concentrations of 0, 100, 200 or 600 ppm. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of rats equals approximately 0.05 mg/kg/day. Therefore, these dietary levels have been calculated to correspond approxima[illegible] to 0, 2.5, 5.0 or 15.0 mg/kg/day. No treatment-related effects [illegible]ported on survival, body weight gain, food consumption, organ weights, organ-to-body weight ratios, hematological, blood chemistry or urinary parameters, liver and kidney function tests or gross and histopathological observations. Based on this information, a NOAEL of 600 ppm (15 mg/kg/day; the highest dose tested) was identified.

Reproductive Effects

- In a three-generation reproduction study, Holsing (1968b) administered carboxin (technical D-735; 97% active ingredient) to Charles River rats (10 males/dose, 20 females/dose; controls: 15 males, 30 females) (age not specified) at dietary concentrations of 0, 100, 200 or 600 ppm. Based on the dietary assumptions of Lehman (1959), these dietary levels have been calculated to correspond to dose levels of approximately 0, 5, 10 or 30 mg/kg/day. Criteria evaluated included fertility, gestation, live birth and lactation indices, litter size and the physical appearance and growth of the pups. No compound-related effects on reproductive performance were reported at any dose level. A compound-related effect on the progeny (moderate growth suppression in the nursing male and female pups of all three generations) was observed at the 600-ppm (30 mg/kg/day) dose level. Based on the information presented in this study, a NOAEL of 200 ppm (10 mg/kg/day) was identified.

Developmental Effects

- Schardein and Laughlin (1981) administered technical Vitavax (carboxin; 99% active ingredient) by gavage at doses of 0, 75, 375 or 750 mg/kg/day to seven- to eight-month-old Dutch Belted rabbits (10/dose) on days 6 through 27 of gestation. The compound was administered in a 0.5% carboxymethyl cellulose vehicle. No treatment-related effects on maternal mortality, appearance, behavior or body weight were reported. Four females aborted on days 27 and 28 of gestation (one at 375 mg/kg/day, three at 750 mg/kg/day). Examination for fetal malformations revealed no compound-related differences between the control and treatment groups. Based on the frequency of abortion, a NOAEL of 75 mg/kg/day and a LOAEL of 375 mg/kg/day were identified.

- Knickerbocker (1977) administered carboxin (technical Vitavax; purity not specified) in corn oil by gavage at doses of 0, 4, 20 or 40 mg/kg/day to sexually mature (age not specified) Sprague-Dawley rats (20/dose) on days 6 through 15 of gestation. No compound-related effects were observed on reproduction, gestation or in skeletal or soft tissue development. Based on the information presented, a NOAEL of 40 mg/kg/day (the highest dose tested) was identified.

Mutagenicity

- Brusick and Weir (1977) conducted a mutagenicity assay using *Salmonella typhimurium* strains TA 1535, 1537, 1538, 98 and 100, and *Saccharomyces cerevisiae* strain D4. Carboxin (purity not specified) was tested without activation at concentrations up to 500 ug/plate and with activation at concentrations up to 100 ug/plate. No mutagenic activity was detected in this assay.

- Byeon et al. (1978) reported that carboxin (Vitavax; purity not specified) tested at concentrations up to 1 mg/plate was not found to be mutagenic in an Ames assay using S. typhimurium strains TA 1535, 1538, 98 and 100.

- Brusick and Rabenold (1982) conducted an Ames assay using technical carboxin (Vitavax, 98% active ingredient) at concentrations up to 5,000 ug/plate. No mutagenic activity was detected, with or without activation, in S. typhimurium strains TA 1535, 1537, 1538, 98 and 100.

- Myhr and McKeon (1982) reported the results of a primary rat hepatocyte unscheduled DNA synthesis assay using carboxin (technical Vitavax; 98% active ingredient). The test compound produced significant increases in the nuclear labeling of primary rat hepatocytes over a concentration range of 5.13 to 103 ug/mL.

Carcinogenicity

- Holsing (1969a) administered carboxin (technical D-735; considered to be 100% active ingredient) to Charles River rats (30/sex/dose; controls: 60/sex, for 2 years at dietary concentrations of 0, 100, 200 or 600 ppm. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of rats equals approximately 0.05 mg/kg/day. While the age of the animals was not specified, the weights of the male rats at initiation ranged from 65 to 88 g and the weights of the female rats ranged from 59 to 85 g. Therefore, dietary levels correspond to approximately 0, 5, 10 or 30 mg/kg/day. No evidence of increased tumor frequency was detected by either gross or histological examination of tissues.

- Jessup et al. (1982) administered carboxin (technical Vitavax; purity not specified) to six-week-old Charles River CD-1 mice (50/sex/dose; controls: 75/sex) for approximately 84 weeks at dietary concentrations of 0, 50, 2,500 or 5,000 ppm. The authors indicated that these dietary levels corresponded to dosage levels of approximately 0, 8, 385 or 751 mg/kg/day for males and 0, 9, 451 or 912 mg/kg/day for females. Survival rates of females receiving 5,000 ppm (912 mg/kg/day) were significantly (p <0.01) lower than those of controls. No compound-related gross pathologic lesions were observed at necropsy in any treatment group. Microscopically, compound-related effects on the liver, consisting of hypertrophy of the centrilobular parenchymal cells, were observed in mice in the 2,500 or 5,000 ppm dose groups (385 and 751 mg/kg/day for males; 451 and 912 mg/kg/day for females). In males, the incidence of pulmonary adenoma/alveolar-bronchiolar adenoma was 13/75, 7/49, 7/50, and 17/50 at 0, 50, 2,500, and 5,000 ppm, respectively. The incidence at the high dose (34%) may have been compound-related based on comparison with the incidence in controls (17%). The difference was statistically significant (p <0.01) using Cox's test for adjusted trend and the Kruskall Wallis tests for life-table data and adjusted incidence. However, based on the opinions of pathologists who reviewed the data and on historical data on tumor incidence in control Charles River CD-1 mice, the authors concluded that the increased incidence was not compound-related. Historical data indicate that in six 18-month studies, the incidence of lung adenomas ranged from 6.3 to

16.7%; in seven 20- to 22-month studies, the incidence of lung adenomas ranged from 4.0 to 31.1%.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

Appropriate data for calculating a One-day HA value are not available. It is recommended that the Longer-term HA value for the 10-kg child (1.0 mg/L, calculated below) be used as the One-day HA value.

Ten-day Health Advisory

Appropriate data for calculating a Ten-day HA value are not available. The 22-day rabbit teratogenicity study by Schardein and Laughlin (1981) was considered for the development of the Ten-day HA. However, the NOAEL (75 mg/kg/day) identified in this study is far in excess of the NOAEL (10 mg/kg/day) identified in the 90-day rat feeding study reported by Ozer (1966) suggesting that the rat is the more sensitive species. It is, therefore, recommended that the Longer-Term HA value for the 10-kg child (1.0 mg/L, calculated below) be used as the Ten-day value.

Longer-term Health Advisory

The study by Ozer (1966) has been selected to serve as the basis for calculating the Longer-term HA for carboxin. In this study, weanling rats were exposed to carboxin in the diet for 90 days. At 30 mg/kg/day there was histological evidence of renal injury. At 10 mg/kg/day, no effects were detected on any parameter measured, including growth, hematology, blood chemistry, urinalysis, gross pathology and histopathology. Based on these data, a NOAEL of 10 mg/kg/day was identified. This value is supported by the subchronic (84 week) feeding study in mice by Jessup et al. (1982) which identified a NOAEL of 8 to 9 mg/kg/day, based on the absence of effects on appearance, behavior, mortality, weight gain, hematology, gross pathology and histopathology.

The Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(10 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 1.0 \text{ mg/L } (1{,}000 \text{ ug/L})$$

where:

10 mg/kg/day = NOAEL, based on absence of effects on growth, hematology, blood chemistry, urinalysis, gross pathology and histopathology in rats exposed to carboxin in the diet for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(10 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 3.5 \text{ mg/L } (4{,}000 \text{ ug/L})$$

where:

10 mg/kg/day = NOAEL, based on absence of effects on growth, hematology, blood chemistry, urinalysis, gross pathology and histopathology in rats exposed to carboxin in the diet for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose

(RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Holsing (1969a) has been selected to serve as the basis for calculation of the Lifetime HA for carboxin. In this study, rats were exposed to carboxin in the diet for 2 years. At 10 mg/kg/day, no significant effects were detected on appearance, behavior, body weight, mortality, hematology, blood chemistry, urinalysis, gross pathology or histopathology. Based on these data, a NOAEL of 10 mg/kg/day was identified. This value is supported by a 90-day rat study (Ozer, 1966) which also identified a NOAEL of 10 mg/kg/day, a 2-year feeding study in dogs by Holsing (1969b) which identified a NOAEL of 15 mg/kg/day, and an 84-week mouse study (Jessup et al., 1982) which identified a NOAEL of 8 mg/kg/day for males and 9 mg/kg/day for females.

Using the NOAEL of 10 mg/kg/day, the Lifetime HA for carboxin is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(10\ \text{mg/kg/day})}{(100)} = 0.1\ \text{mg/kg/day}$$

where:

10 mg/kg/day = NOAEL, based on absence of effects on appearance, behavior, body weight, mortality, hematology, blood chemistry, urinalysis, gross pathology or histopathology in rats exposed to carboxin in the diet for 2 years.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} \quad \frac{.\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 3.5\ \text{mg/L}\ (4{,}000\ \text{ug/L})$$

where:

0.1 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (3.5 mg/L) (20%) = 0.7 mg/L (700 ug/L)

where:

3.5 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Jessup et al. (1982) reported a possible compound-related increase in pulmonary adenoma/alveolar-bronchiolar adenoma frequency in male CD-1 mice that received carboxin in the diet at 751 mg/kg/day.

- Holsing (1969a) fed Charles River rats carboxin at dietary levels up to 30 mg/kg/day for 2 years, and detected no compound-related histopathologic changes. This study is limited, however, by the following factors: inadequate numbers of animals were used; survival was generally poor and, therefore, late-developing lesions may not have been detected; all tissues from all animals were not examined microscopically; and there was no adjustment in dietary levels of carboxin to account for growth of the test animals.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of carboxin.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), carboxin is classified in Group D: not classified. This category is for substances with inadequate human and animal evidence of carcinogenicity or for which no data are available.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- No existing criteria or standards for oral exposure to carboxin were located.

- The U.S. EPA (OPP) has proposed an Acceptable Daily Intake (ADI) of 0.4 mg/kg/day, based on a NOAEL of 200 ppm established in a 2-year rat feeding study and an uncertainty factor of 100 (U.S. EPA, 1981).

- The U.S. EPA has established residue tolerances for carboxin in or on raw agricultural commodities that range from 0.01 to 0.5 ppm (CFR, 1979).

VII. ANALYTICAL METHODS

- Analysis of carboxin is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. The method detection limit has not been determined for carboxin but it is estimated that the detection limits for analytes included in this method are in the range of 0.1 to 2 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information regarding treatment techniques to remove carboxin from contaminated waters is currently available.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

CHLORAMBEN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

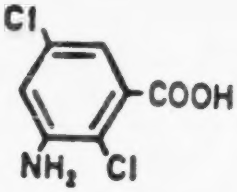
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No.: 133-90-4

Structural Formula:



3-Amino-2-5-dichlorobenzoic acid

Synonyms

- Acp-m-728, Ambiben; Abiben; Amibin; Amoben; Chlorambed; Chlorambene; NCI-C00055 ornamental weeder; Ornamental weeder; Vegaben; Vegiven (U.S. EPA, 1985).

Uses

- Preemergent herbicide for weed control (Meister, 1983).

Properties (U.S. EPA, 1985; CHEMLAB, 1985)

Chemical Formula	$C_7H_5O_2NCl_2$
Molecular Weight	206.02
Physical State (25°C)	Crystals
Boiling Point	--
Melting Point	200-201°C
Density	--
Vapor Pressure	7×10^{-3} mm Hg (100°C)
Specific Gravity	--
Water Solubility (25°C)	700 mg/L
Log Octanol/Water Partition Coefficient	2.32
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Chloramben has been found in 13 of 34 surface water samples anaylzed and in 1 of 566 ground water samples (STORET, 1988). Samples were collected at 11 surface water locations and 322 ground water locations, and chloramben was found in only 1 state. The 85th percentile of all non-zero samples was 2.1 ug/L in surface water and 1.7 ug/L in ground water sources. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Sodium chloramben appears to be resistant to hydrolysis. Limited studies indicate that there is no loss of phytotoxicity when aqueous solutions of chloramben are kept in the dark (Registration Standard Science Chapter for Chloramben).
- Photodegradation of aqueous solutions of sodium chloramben appears to occur readily in sunlight. Total loss of phytotoxicity occurs in 2 days. Loss of phytotoxicity on dry soil is somewhat slower, about about 30% in 48 hours (Registration Standard Science Chapter for Chloramben).
- Soil bacteria bring about a loss of phytotoxicity in sodium chloramben after several weeks. It appears that this is due to a decarboxylation. The rate of reaction appears to be independent of soil pH within the range of 4.3 to 7.5 (Registration Standard Science Chapter for Chloramben).
- The mobility of sodium chloramben is governed principally by its high solubility in water and its apparent limited strength of adsorption to soil particles. It appears to easily leach down in most soil types by rainfall (Registration Standard Science Chapter for Chloramben).
- Probably all plants grown in contact with sodium chloramben take up the compound. In some plants the subsequent movement of compound away from the roots is very slow, whereas in others it readily spreads throughout the plant. The fate of chloramben in plants includes decomposition, a detoxifying conjugation which proceeds fairly rapidly, or a detoxifying conjugation which goes slowly, if at all (Registration Standard Science Chapter for Chloramben).
- The methyl ester of chloramben acid appears to have the expected properties of a carboxylic acid ester. It is apparently not hydrolysed after a short period in contact with water at slightly acid pH values (5 to 6). Bacteria-mediated hydrolysis appears to be quick: approximately 50% of the ester is converted to the free acid in about 1 week when in contact with wet soil. A subsequent and slower bacterial reaction, shown by a loss of phytotoxicity, is probably a decarboxylation, as with sodium chloramben (Registration Standard Science Chapter for Chloramben).
- The leaching behavior of the methyl ester is governed by its aqueous solubility, which is much lower than that of the sodium salt (120 ppm and 250,000 ppm, respectively). For a given rainfall the ester seems to leach down about 15% of the distance travelled by the sodium salt (Registration Standard Science Chapter for Chloramben).

III. PHARMACOKINETICS

Absorption

- Chloramben is rapidly absorbed from the gastrointestinal tract of Sprague-Dawley female rats (Andrawes, 1984). Based on radioactivity recovered in urine (96.7%) and expired air (0.2%), about 97% of an oral dose (5 uCi/rat) of chloramben is absorbed.

Distribution

- Andrawes (1984) reported low levels (up to 0.5% of the administered dose) of chloramben in liver, kidney, lung, muscle, plasma and red blood cells of rats 96 hours after a single oral dose (by gavage).

Metabolism

- In rats dosed by gavage, Andrawes (1984) reported that the parent compound accounted for 70% of the applied dose in 24-hour urine.

- Andrawes (1984) identified 5 of 24 urinary metabolites: 3-amino-5-chlorobenzoic acid; 3-aminobenzoic acid; 2,5-dihydroxybenzoic acid; 3,5-dihydroxybenzoic acid; and 2,5-dichloroaniline. Together, these constituted 1.4% of the administered dose.

- Metabolism of chloramben in rats proceeded through dechlorination, deamination, decarboxylation and hydroxylation. Metabolism through oxidative ring cleavage was negligible (Andrawes, 1984).

Excretion

- Rats administered chloramben (5 uCi/rat) by gastric intubation excreted over 99% of the dose within 3 to 4 days, mostly within the first 24 hours (Andrawes, 1984). Approximately 96.7% was eliminated in the urine, with lesser amounts in the feces (4.1%) and respiratory gases (0.2%). Only 0.6% remained in the carcass after 3 to 4 days.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the human health effects of chloramben.

Animals

Short-term Exposure

- Acute oral LD_{50} values for chloramben range from 2,101 mg/kg (Field, 1980) to 5,000 mg/kg (Field and Carter, 1978) in rats; the acute dermal LD_{50} in rabbits has been reported to be >2,000 (Field and Field, 1980) or >5,000 mg/kg (Field, 1978).

- Rees and Re (1978) reported an acute (1 hr) LC_{50} of >200 mg/L in rat inhalation studies.

- Keller (1959) fed male Holtzman Sprague-Dawley rats (10/dose) chloramben (100% a.i.) for 28 days in the diet at dose levels of 0, 1,000, 3,000 or 10,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 50, 150 or 500 mg/kg/day. Body weights, food consumption, general appearance and behavior and histopathology were evaluated. There were no statistically significant differences between the treated rats and untreated controls in any parameter measured. Based on this information, a No-Observed-Adverse-Effect Level (NOAEL) of 10,000 ppm (500 mg/kg/day), the highest dose tested, was identified.

Dermal/Ocular Effects

- Gabriel (1969) applied chloramben (4 to 8 g/kg) to intact and abraded skin of 16 male albino rabbits (8/dose). Test animals were observed for 14 days. No evidence of skin irritation was observed under conditions of the study.

- In a study by Myers et al. (1982), a 1.0% (w/w) chloramben sodium salt suspension produced little or no sensitization reactions in male albino Hartley guinea pigs.

Long-term Exposure

- In studies by Beliles (1976), weanling Golden Syrian hamsters (12/sex/dose) were administered technical chloramben (purity not specified) at dose levels of 0, 100, 1,000 or 10,000 ppm (reported to be equivalent to 0, 11, 115 and 1,070 mg/kg/day) in the diet for 90 days. Food consumption, body and organ weights and histopathology were evaluated. No treatment-related adverse effects were reported for any parameter evaluated. Based on this information, a NOAEL of 10,000 ppm (1,070 mg/kg/day), the highest dose tested, was identified.

- In an 18-month feeding study (Huntingdon Research Center, 1978; cited in U.S. EPA, 1981), Crl:COBS CD-1 mice (50/sex/dose) were administered technical chloramben (purity not specified) at dietary levels of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 15, 150 and 1,500 mg/kg/day. No compound-related effects were observed in terms of survival, general appearance, behavior or changes in body weight. Statistically significant ($p < 0.05$) changes in organ weights included decreased liver weight in males at 100 ppm, decreased kidney weight in males at 10,000 ppm, and decreased kidney weight in females at 10,000 ppm. Since the values for these observations were within normal ranges for this species and no trends were established, the organ weight changes were not attributed to compound administration. Histopathological examinations revealed alterations in the livers of all treated mice. The primary hepatocellular reaction was a histomorphological hepatocellular alteration compatible with that observed in enzyme induction. The typical cellular changes included hepatocyte hypertrophy, increased nuclear size and chromatin content, and dense granular eosinophilic cytoplasm. Other changes included scattered foci of individual or small groups of degenerating hepatocytes, hepatocyte vacuolation, cytoplasmic eosinophilic inclusions, and multiple focal small granulomas. Based on the reported hepatic effects, this study identifies a Lowest-Observed-Adverse-Effect Level (LOAEL) of 100 ppm (15 mg/kg/day).

- NCI (1977) administered technical-grade chloramben (90 to 95% active ingredient) to Osborne-Mendel rats (50/sex/dose) and B6C3F$_1$ mice (50/sex/dose) for 80 weeks at dietary levels of 10,000 or 20,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day and 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of 500 or 1,000 mg/kg/day for rats and 1,500 or 3,000 mg/kg/day for mice. Matched controls consisted of 10 animals per sex for each species. Pooled controls consisted of the matched controls plus 75 rats/sex and 70 mice/sex from similarly performed bioassays. Body weights and mortality did not differ between control and treatment groups for both species, and the various (unspecified) clinical signs observed were similar in the control and treatment groups for both species. Based on this information, a NOAEL of 20,000 ppm (1,000 mg/kg/day for rats and 3,000 mg/kg/day for mice), the highest dose tested, was identified for each species.

- In studies conducted by Paynter et al. (1963), albino rats (35/sex/dose) were administered chloramben (97% pure) in the diet for 2 years at dose levels of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 5, 50 or 500 mg/kg/day. Untreated rats (70/sex/dose) were observed concurrently. The general appearance and behavior, growth, food consumption, clinical chemistry, hematology and histopathology in the treated rats did not differ significantly from the untreated controls. Based on this information, a NOAEL of 10,000 ppm (500 mg/kg/day), the highest dose tested, was identified.

- Hazleton and Farmer (1963) administered technical chloramben (97% pure) in the feed to 16 young adult beagle dogs (4/sex/dose) for 2 years at dietary levels of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 2.5, 25 or 250 mg/kg/day. General appearance and behavior, food consumption, body weight, hematology, biochemistry, urinalysis and histopathology of the treated dogs did not differ significantly from the untreated controls. Based on this information, a NOAEL of 10,000 ppm (250 mg/kg/day), the highest dose tested, was identified.

- Johnson and Seibold (1979) administered technical chloramben to Sprague-Dawley rats for 2 years at dietary concentrations of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959) this corresponds to doses of 0, 5, 50 and 500 mg/kg/day. No compound-related effects were observed on any parameters measured including body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology and histopathology. Based on this information, a NOAEL of 10,000 ppm (500 mg/kg/day), the highest dose tested, was identified.

Reproductive Effects

- In a three-generation study (Gabriel, 1966), three groups of albino rats (8 females and 16 males/dose) were administered 0, 500, 1,500 or 4,500 ppm chloramben (purity not specified) in the diet for 9 weeks prior to breeding, during breeding and during weaning periods. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these dietary levels correspond to doses of about 0, 25, 75 or 225 mg/kg/day. Untreated animals served as controls. Following treatment, various parameters were measured, including indices of fertility, gestation, viability and lactation. No adverse effects were reported in any parameter measured. Based on this information, a NOAEL of 4,500 ppm (225 mg/kg/day), the highest dose tested, was identified for reproductive effects.

Developmental Effects

- Beliles and Mueller (1976) administered technical chloramben (purity not specified) to pregnant CFE rats (20/dose) by incorporation into the diets on days 6 through 15 of gestation. No compound-related changes were seen among dams treated at levels of 0, 500, 1,500 and 4,500 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 25, 75 or 225 mg/kg/day. Fetal mortality was increased, and data suggestive of decreased fetal skeletal development were observed in fetuses from dams treated at 4,500 ppm (225 mg/kg/day). At 1,500 ppm (75 mg/kg/day), there was no significant increase in embryo mortality; however, there was a generalized reduction in skeletal development. Fetuses of dams treated with 500 ppm (25 mg/kg/day) were similar in all respects to those of untreated control dams. Based on this information, a NOAEL of 4,500 ppm (225 mg/kg/day), the highest dose tested, was identified for maternal toxicity and teratogenicity. The NOAEL for fetotoxicity was identified as 500 ppm (25 mg/kg/day).

- Holson (1984) conducted studies in which New Zealand White rabbits (24/dose) were administered chloramben (sodium salt, 83% a.i. by weight) by gavage at dose levels of 0, 250, 500 or 1,000 mg/kg during days 6 through 18 of gestation. A NOAEL of 1,000 mg/kg/day, the highest dose tested, was identified, since the test compound did not produce maternal or fetal toxicity or teratogenic effects at any dose level tested. Other end points were not monitored.

Mutagenicity

- Chloramben was found to be negative in several indicator systems for potential mutagenic activity, including several microbial assays (Anderson et al., 1967; Eisenbeis et al., 1981; Jagannath, 1982), an *in vivo* bone marrow cytogenetic assay (Ivett, 1985) and primary rat hepatocytes unscheduled DNA synthesis test (Myhr and McKeon, 1982).

- Results were positive for the in vitro cytogenic test using Chinese hamster ovary cells (Galloway and Lebowitz, 1982).

Carcinogenicity

- In an 18-month feeding study (Huntingdon Research Center, 1978; cited in U.S. EPA, 1981), Crl:COBS CD-1 mice (50/sex/dose) were administered technical chloramben (purity not specified) at dietary levels of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 15, 150 and 1,500 mg/kg/day. Hepatocellular carcinomas (trabecular type) were present in 1/50 low-dose and 1/50 high-dose males. In no case was vascular invasion or secondary spread of the nodular carcinoma masses observed. Hepatocellular adenomas were present only in males as follows: 5/50 control, 2/50 low-dose, 2/48 intermediate-dose and 5/50 high-dose. However, due to a number of deficiencies in this study (e.g., missing data, significant tissue autolysis), no conclusion can be made regarding the oncogenic potential of the test material.

- NCI (1977) administered 10,000 or 20,000 ppm technical chloramben (90-95% active ingredient) in the feed to Osborne-Mendel rats (50/sex/dose) and B6C3F$_1$ mice (50/sex/dose) for 80 weeks followed by up to 33 weeks of postexposure observation. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day and 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of 500 or 1,000 mg/kg/day for rats and 1,500 or 3,000 mg/kg/day for mice. Under conditions of the study, no compound-related tumors were reported in male or female rats or male mice. Hepatocellular carcinomas were reported in female mice, but in a retrospective audit of this bioassay by Drill et al. (1982), it was reported that the incidence of hepatocellular carcinomas in both the low-dose and high-dose female mice was lower than the maximal incidence of corresponding tumors in historical groups. It was concluded that there was no association between chloramben and the occurrence of hepatocellular carcinomas under conditions of the assay. However, since exposure was for only 80 weeks, this study may not have been adequate to detect late-occurring tumors.

- Paynter et al. (1963) reported no evidence of carcinogenic activity in albino rats (35/sex/dose) that received chloramben (97% pure) in the diet for 2 years at dose levels of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959) this corresponds to doses of 0, 5, 50 or 500 mg/kg/day.

- Johnston and Seibold (1979) reported no evidence of carcinogenic activity in Sprague-Dawley rats administered 0, 100, 1,000 or 10,000 ppm technical chloramben in the diet for 2 years. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 5, 50 or 500 mg/kg/day. No compound-related effects were observed on any other parameters measured, including body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology and histopathology.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were found in the available literature that were suitable for determination of the One-day HA value. It is, therefore, recommended that the Ten-day HA value for a 10-kg child (3 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-Day Health Advisory

The rat teratology study by Beliles and Mueller (1976) has been selected to serve as the basis for determination of the Ten-day HA value for a 10-kg child for chloramben. In this study, a NOAEL of 225 mg/kg/day, the highest dose tested, was identified for maternal toxicity and teratogenicity while a NOAEL of 25 mg/kg/day was identified for fetotoxicity (skeletal development) in rats exposed on days 6 to 15 of gestation. There is some question as to whether it is appropriate to base a Ten-day HA for the 10-kg child on fetotoxicity observed in a teratology study. However, this study is of appropriate duration and the fetus may be more sensitive than the 10-kg child.

The studies by Keller (1959) and Holson (1984) have not been selected, since the NOAEL values identified in these studies (500 and 1,000 mg/kg/day, respectively) are much higher than the NOAEL identified by Beliles and Mueller (1976).

Using the NOAEL of 25 mg/kg/day, the Ten-day HA for the 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(25 \text{ mg/kg/day}) \ (10 \text{ kg})}{(100) \ (1 \text{ L/day})} = 2.5 \text{ mg/L } (3{,}000 \text{ ug/L})$$

where:

25 mg/kg/day = NOAEL, based on the absence of systemic toxic effects in rats fed chloramben for 10 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisories

No data were found in the available literature that were suitable for the determination of the Longer-term HA. It is, therefore, recommended that an adjusted DWEL for a 10 kg child (0.15 mg/L = 200 ug/L) and the DWEL for a a 70-kg adult (0.525 mg/L = 500 ug/L) be used at this time for the Longer-term HA values.

$$\text{Adjusted DWEL} = \frac{(0.015\ \text{mg/kg/day})\ (10\ \text{kg})}{(1\ \text{L/day})} = 0.15\ \text{mg/L}\ (200\ \text{ug/L})$$

where:

0.015 mg/kg/day = RfD.

10 kg = assumed body weight of a child.

1 L/day = assumed daily water consumption of a child.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 18-month feeding study by the Huntingdon Research Center (1978; cited in U.S. EPA, 1981) has been selected to serve as the basis for determination of the Lifetime HA for chloramben. In this study, Crl:COBS CD-1 mice were administered technical chloramben at dietary levels of 0, 100, 1,000 or 10,000 ppm (0, 15, 150 or 1,500 mg/kg/day). Hepatocellular alterations were observed in mice in all treatment groups, and a LOAEL of 100 ppm (15 mg/kg/day) was identified. Other studies of appropriate duration identify NOAELs that are higher than the LOAEL of 15 mg/kg/day. For example, Hazleton and Farmer (1963) identified a NOAEL of 250 mg/kg/day in a 2-year study in dogs, and both Paynter et al. (1963) and Johnston and Siebold (1979) identified a NOAEL of 500 mg/kg/day in 2-year rat studies.

Using the LOAEL of 15 mg/kg/day, the Lifetime HA for chloramben is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(15\ \text{mg/kg/day})}{(1{,}000)} = 0.015\ \text{mg/kg/day}$$

where:

15 mg/kg/day = LOAEL, based on hepatic effects in mice exposed to chloramben via the diet for 18 months.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.015\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.525\ \text{mg/L}\ (500\ \text{ug/L})$$

where:

0.015 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.525\ \text{mg/L})\ (20\%) = 0.105\ \text{mg/L}\ (100\ \text{ug/L})$$

where:

0.525 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- NCI (1977) evaluated the carcinogenic potential of orally administered chloramben (10,000 or 20,000 ppm, equivalent to 500 or 1,000 mg/kg/day) to Osborne-Mendel rats (50/sex/dose) and B6C3F$_1$ mice (20/sex/dose) for 80 weeks. It was concluded in a retrospective audit of this assay (Drill et al., 1982) that under conditions of this study, chloramben is not carcinogenic. Since exposure was for only 80 weeks, this experiment may not have been adequate to detect late-occurring tumors. Johnson and Seibold (1979) reported no evidence of carcinogenic activity in Sprague-Dawley rats that received chloramben in the diet for 2 years at concentrations up to 500 mg/kg/day. The Huntingdon Research Center (1978; cited in U.S. EPA, 1981) reported no evidence of carcinogenicity in Crl:COBS CD-1 mice that received chloramben in the diet for 18 months at concentrations up to 1,500 mg/kg/day. However, due to a number of deficiencies in this study, no conclusion can be made regarding the oncogenic potential of the test material. Paynter et al. (1963) reported no evidence of carcinogenicity in albino rats that received chloramben in the diet for 2 years at concentrations up to 500 mg/kg/day.

- The International Agency for Research on Cancer has not evaluated the carcinogenicity of chloramben.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), chloramben may be classified in Group D: not classified. This category is for agents with inadequate human and animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- NAS has determined an Acceptable Daily Intake of 0.25 mg/kg/day with a suggested-no-adverse-effect level of 1.75 mg/L (U.S. EPA, 1985).

- The U.S. EPA has established a residue tolerance for chloramben in or on raw agricultural commodities of 0.1 ppm (40 CFR 180.226).

VII. ANALYTICAL METHODS

- Chloramben may be analyzed using a gas chromatographic (GC) method applicable to the determination of chlorinated acid, ethers and in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is acidified. The compounds are extracted with ethyl ether using a separatory funnel. The derivatives are hydrolyzed with potassium hydroxide, and extraneous organic material is removed by a solvent wash. After acidification, the acids are extracted and converted to their methyl esters using diazomethane as the derivatizing agent. Excess reagent is removed, and the esters are determined by electron-capture (EC) gas chromatography. The method detection limit has not been determined for this compound.

VIII. TREATMENT TECHNOLOGIES

- No data were found for the removal of chloramben from drinking water by conventional treatment.

- No data were found for the removal of chloramben from drinking water by activated carbon treatment. However, due to its low solubility and its high molecular weight, chloramben probably would be amenable to activated carbon adsorption.

- No data were found for the removal of chloramben from drinking water by ion exchange. However, chloramben is an acidic pesticide and these compounds have been readily adsorbed in large amounts by ion exchange resins. Therefore, chloramben probably would be amenable to an ion exchange.

- No data were found for the removal of chloramben from drinking water by aeration. However, the Henry's Coefficient can be estimated from available data on solubility (700 mg/L at 25°C) and vapor pressure (7×10^{-3} mm Hg at 100°C). Due to its estimated Henry's Coefficient of 0.15 atm, chloramben probably would not be amenable to aeration or air stripping.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

CHLOROTHALONIL

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

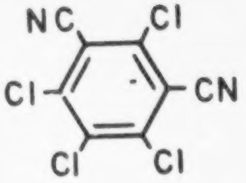
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1897-45-6

Structural Formula



2,4,5,6-Tetrachloro-1,3-benzenedicarbonitrile

Synonyms

- Tetrachloroisophthalonitrile; Bravo; Chloroalonil; Chlorthalonil; Daconil; Exothern; Forturf; Nopcocide N96; Sweep; Termil; TPN; DAC-2787; T-117-11; DTX-77-0033; DTX-77-0034; DTX-77-0035.

Uses (Meister, 1986)

- Broad-spectrum fungicide.

Properties (Meister, 1986; CHEMLAB, 1985; Meister, 1983; Windholz et al., 1983)

Chemical Formula	$C_8N_2Cl_4$
Molecular Weight	265.89
Physical State (25°C)	White, crystalline solid
Boiling Point	350°C
Melting Point	250 to 251°C
Density	--
Vapor Pressure (40°C)	2.0×10^{-6} mm Hg at 25°C
Specific Gravity	--
Water Solubility (25°C)	1.2 mg/L at 25°C
Octanol/Water Partition Coefficient	7.62×10^2
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Chlorothalonil has been found in 1 of 4 surface water samples analyzed from 3 surface water stations and in none of the 633 ground water samples (STORET, 1988). Samples were collected at 3 surface water locations and 627 ground water locations; and at the 1 location where it was found in Missouri, the concentration was 6,500 ug/L. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Ring-labeled ^{14}C-chlorothalonil, at 0.5 to 1.5 ppm, was stable to hydrolysis for up to 72 days in aqueous solutions buffered at pH 5 and 7 (Szalkowski, 1976b). At pH 9, chlorothalonil hydrolyzed with half-lives of 33 to 43 days and 28 to 72 days in solutions to which ring-labeled ^{14}C-chlorothalonil was added at 0.52 and 1.5 ppm, respectively. After 72 days of incubation, pH 9-buffered solutions treated with chlorothalonil at 1.5 ppm contained 36.4% chlorothalonil, 48.9% 3-cyano-2,4,5,6-tetrachlorobenzamide (DS-19211) and 11.3% 4-hydroxy-2,5,6-trichloroisophthalonitrile (DAC-3701).

- At 1,000 ppm, the chlorothalonil degradation product, ^{14}C-DAC-3701, was not hydrolysed in aqueous solutions buffered at pH 5, 7, and 9 after 72 days of incubation (Szalkowski, 1976b).

- Ring-labeled ^{14}C-chlorothalonil and its major degradate, ring-labeled ^{14}C-DAC-3701, were stable to photolysis on two silt loam and three silty clay loam soils, after UV irradiation for the equivalent of 168 12-hour days of sunlight (Szalkowski, undated).

- 14C-Chlorothalonil is degraded with half-lives of 1 to 16, 8 to 31, and 7 to 16 days in nonsterile aerobic sandy loam, silt loam and peat loam soils, respectively, at 77 to 95°F and 80% of field moisture capacity (Szalkowski, 1976a). When chlorothalonil (WP) was applied to nonsterile soils ranging in texture from sand to silty clay loam, at 76 to 100°F and 6% soil moisture, it was degraded with half-lives of 4 to more than 40 days; increasing either soil moisture content (0.6 to 8.9%) or incubation temperature (76 to 100°F) enhanced chlorothalonil degradation (Stallard and Wolfe, 1967). Soil pH (6.5 to 8) does not appear to influence or only negligibly influences the degradation rate of chlorothalonil; however, soil sterilization greatly reduced the degradation rate. The major degradate identified in nonsterile aerobic soil was DAC-3701, representing up to 69% of the applied radioactivity. Other identified degradates included DS-19221, trichloro-3-carboxybenzamide, 3-cyanotrichlorohydroxybenzamide, and 3-cyanotrichlorobenzamide (Stallard and Wolfe, 1967; Szalkowski, 1976a; Szalkowski et al., 1979).

- ^{14}C-Chlorothalonil was immobile (R_f 0.0) and the degradate ^{14}C-DAC-3701 was found to have low to intermediate mobility (R_f 0.25 to 0.43) in two silt loam and three silty clay loam soils, as evaluated using soil thin-layer chromotography (TLC) (Szalkowski, undated). Based on batch equilibrium tests, chlorothalonil has a relatively low mobility (high adsorption) in silty clay loam (K = 26), silt (K = 29), and sandy loam (K = 20) soils but is intermediately mobile (low adsorption) in a sand (K = 3) (Capps et al., 1982). Soil organic matter content did not appear to influence the mobility of chlorothalonil in soil.

- The chlorothalonil degradate DAC-3701 is mobile in sand, loam, silty clay loam and clay soils (Wolfe and Stallard, 1968a). After eluting a 6-in soil column with the equivalent of 5 inches of water, approximately 57, 84, 10 and 84% of the applied DAC-3701 was recovered in the leachate of the sand, loam, silty clay loam and clay soil columns, respectively.

- Chlorothalonil (4.17 lb/gal FlC) was degraded with a half-life of 1 to 3 months in sandy loam and silt loam soils when applied alone at 8.34 lb ai/A or in combination with benomyl (50% wettable powder) at 1.35 lb ai/A (Johnston, 1981). The treated soils were maintained at 80% of moisture capacity in a greenhouse.

- Under field conditions, the half-life of chlorothalonil (75% wettable powder) in a sandy loam soil was between 1 and 2 months following the last of five consecutive weekly applications totaling 15 lb ai/A (Stallard et al., 1972). Little movement of chlorothalonil (0.01 to 0.17 ppm) below the 0- to 3-inch depth occurred throughout the 8-month study. Small amounts (0.01 to 0.21 ppm) of the degradate DAC-3701 were found in soil samples collected up to 5 months post-treatment. No chlorothalonil or DAC-3701 was detected (less than 1 ppb) in a nearby stream up to 7 months post-treatment, or in ground water samples (10-foot depth) up to 8 months post-treatment. Cumulative rainfall over the study period was 26.22 inches.

III. PHARMACOKINETICS

Absorption

- Ryer (1966) administered ^{14}C-chlorothalonil (dose not specified) orally to albino rats (3/sex; strain not specified). In 48 hours post-treatment, 60% of the radioactivity was detected in the feces, suggesting that at least 40% of the oral dose was absorbed.

- Skinner and Stallard (1967) reported that rats receiving 1.54 mg of ^{14}C-chlorothalonil (containing 2.8 uCi) in a 500 mg/kg dose (route not specified) eliminated 88% of the administered dose unchanged in the feces over 264 hours, suggesting that 12% was absorbed.

- Skinner and Stallard (1967) reported that mongrel dogs receiving a single oral dose (by capsule) of 500 mg/kg of chlorothalonil, eliminated 85% of the administered dose as the parent compound within 24 hours post-treatment, suggesting that 15% was absorbed.

Distribution

- Ryer (1966) administered ^{14}C-chlorothalonil (dose not specified) to albino rats (3/sex; strain not specified) by oral intubation. After 11 days, the carcasses retained 0.44% of the dose while 0.05% of the dose remained in the gastrointestinal tract. The highest residues occurred in the kidneys, which averaged 0.01% of the dose for the six rats. Lesser amounts were detected in the eyes, brain, heart, lungs, liver, thyroid and spleen.

- Ribovich et al. (1983) administered single doses of ^{14}C-chlorothalonil by oral intubation to CD-1 mice at levels of 0, 1.5, 15 or 105 mg/kg. Twenty-four hours post-treatment, the stomach, liver, kidneys, fat, small intestine, large intestine, lungs and heart accounted for less than 3% of the administered dose. The stomach and kidneys had the highest concentration at all doses tested. The compound was eliminated from the stomach and kidneys by 168 hours post-treatment.

- Wolfe and Stallard (1968b) reported a study in which dogs and rats received chlorothalonil in the diet for 2 years at 1,500 to 30,000 ppm. The amount of the 4-hydroxy-2,5,6-trichloroisophthalonitrile metabolite that was detected in the kidney tissue of dogs was less than 1.5 ppm; less than 3.0 ppm was detected in liver tissue from dogs and rats. The authors concluded that the metabolite was not stored in animal tissue.

Metabolism

- In the Wolfe and Stallard (1968b) study, only a small amount of the metabolite, 4-hydroxy-2,5,6-trichloroisophthalonitrile, was detected in the kidney tissue of dogs (<1.5 ppm) and in liver tissue from dogs and rats (<3 ppm).

- Marciniszyn et al. (1983b) reported that when Osborne-Mendel rats were administered single oral doses of ^{14}C-chlorothalonil by intubation at levels of 0, 5, 50, 200 or 500 mg/kg, no metabolites of chlorothalonil were unequivocally identified in urine.

Excretion

- The Ryer study (1966) revealed that, at the end of 11 days, an average of 88.45% of the administered dose was excreted in the feces, 5.14% in the urine and 0.32% in expired gases as CO_2.

- Skinner and Stallard (1967) presented results which demonstrated that 88% of a dose (route unspecified) of chlorothalonil was eliminated unchanged in the feces. Only 5.2% was eliminated via the urine and negligible amounts were detected in expired air.

- Ribovich et al. (1983) administered single doses of ^{14}C-chlorothalonil by oral intubation to CD-1 mice at levels of 0, 1.5, 15 or 105 mg/kg. The total recoveries of radioactivity 24 hours post-treatment were 93% for the low dose, 81% for the mid dose and 62% for the high dose. The major route of elimination was the feces and was complete at 24 hours post-treatment for the low- and mid-dose animals, and by 96 hours for the high dose animals.

- Marciniszyn et al. (1981) reported a study in which single doses of ^{14}C-chlorothalonil were administered intraduodenally to male Sprague-Dawley rats at 0.5, 5, 10, 50, 100 or 200 mg/kg. Biliary excretion of radioactivity was monitored for 24 hours. Percent recovery of radioactivity was 27.8, 20.7, 16.8, 6.4, 7.8 and 6% for each dose level, respectively.

- Marciniszyn et al. (1983a) administered ^{14}C-chlorothalonil intraduodenally to male Sprague-Dawley rats (donor animals) at a dose of 5 mg/kg. Bile was collected for 24 hours following administration. Some of the collected bile was administered intraduodenally to recipient rats; bile was also collected from these animals for 24 hours. Data from the donor rats indicated that 1 to 6% of the administered radioactivity was excreted in the bile within 24 hours after dosing. Approximately 19% of the radioactivity in bile administered to recipient rats was excreted within 24 hours after dosing. These data suggest that enterohepatic recirculation plays a role in the metabolism of chlorothalonil in rats.

- Pollock et al. (1983) administered ^{14}C-chlorothalonil by gavage to male Sprague-Dawley rats at dose levels of 5, 50 or 200 mg/kg. They subsequently determined blood concentrations of radioactivity. The authors hypothesized that, at 200 mg/kg, an elimination mechanism (urinary, biliary and/or metabolism) was saturated, since the kinetics were nonlinear at this dose.

IV. HEALTH EFFECTS

- The purity of the administered chlorothalonil is assumed to be $\geq$90% for all studies described below, unless otherwise noted.

Humans

- Johnsson et al. (1983) reported that chlorothalonil exposure resulted in contact dermatitis in 14 of 20 workers involved in woodenware preservation. The wood preservative used by the workers consisted mainly of "white spirit," with 0.5% chlorothalonil as a fungicide. Workers exhibited erythema and edema of the eyelids, especially the upper eyelids, and eruptions on the neck, wrist and forearms. Results of a patch test conducted with 0.1% chlorothalonil in acetone were positive in 7 of 14 subjects. Reactions ranged from a few erythematous papules to marked papular erythema with a brownish hue without infiltration.

Animals

Short-term Exposure

- Powers (1965) reported that the acute oral LD_{50} of chlorothalonil (75% wettable powder) in Sprague-Dawley rats was >10 g/kg.

- Doyle and Elsea (1963) reported that the acute oral LD_{50} of DAC-2787 (chlorothalonil), assumed by authors to be 100%, in male Dublin SD rats was >10 g/kg when the compound was administered in corn oil.

Dermal/Ocular Effects

- Doyle and Elsea (1963) reported that the dermal LD_{50} of DAC-2787 (assumed by the authors to be 100%), applied as a paste made of approximately equal parts of DAC-2787 and corn oil, in albino rabbits was >10 g/kg. At dermal concentrations of 1, 2.15, 4.64 or 10 g/kg (24-hour exposure on abdominal skin), the compound produced mild to moderate skin irritation characterized by erythema, edema, atonia and desquamation.

- Doyle and Elsea (1963) reported that when 3 mg of DAC-2787 (assumed by authors to be 100%, application method unknown) chlorothalonil was applied to the eyes of albino rabbits, eye irritation was limited to mild conjunctivitis that subsided largely or completely within 7 days.

- Auletta and Rubin (1981) reported the results of eye irritation studies in cynomologus monkeys and New Zealand White rabbits using BRAVO 500, a 40% formulation containing 96% pure chlorothalonil. In both species, 0.1 mL of the test substance was instilled into the conjunctival sac of one eye. Each species displayed mild and transient ocular irritation as evidenced by corneal opacities that were reversed by 4 days postinstillation. The animals also showed slight to moderate iridial and conjunctival effects which were also reversible. Rinsing reduced conjunctival and iridial effects and prevented formation of corneal opacities.

Long-term Exposure

- Blackmore and Shott (1968) administered technical DAC 2787 (chlorothalonil), assumed by authors to be 100%, to Charles River rats (50/sex/dose) for 90 days at dietary levels of 0, 4, 10, 20, 30, 40 or 60 ppm (approximately 0, 0.2, 0.5, 1.0, 1.5, 2.0 or 3.0 mg/kg/day; Lehman, 1959). No compound-related effects were reported regarding physical appearance, growth, survival, terminal clinical values, organ weights or organ-to-body weight ratios. Microscopically, the kidneys exhibited occasional vacuolation and swelling of the epithelial cells lining the deeper proximal convoluted tubules. These changes were more numerous and more severe in the two highest dose groups. The authors stated that the difference between the two highest dose groups (2.0 and 3.0 mg/kg/day) and the controls was distinct, but the difference between the lower dose groups and controls was not clear. Based on this information, a NOAEL of 30 ppm (1.5 mg/kg/day) is identified.

- Wilson et al. (1981) administered chlorothalonil (98%) in the diet to Charles River CD rats (20/sex/dose) for 90 days at doses of 0, 40, 80, 175, 375, 750 or 1,500 mg/kg/day. At doses of 375 mg/kg/day or higher, significant decreases in body weight were reported. Decreases in glucose levels, blood urea nitrogen and serum thyroxine were attributed by the investigators to body weight effects. A dose-related decrease in serum glutamic-pyruvic transaminase (SGPT) was noted in all test groups. Significant increases in kidney weights were also noted in males at 40, 80, 175 and 375 mg/kg, while in females increased kidney weights were noted at 80, 175 and 750 mg/kg. These were dose-related increases in kidney-to-body weight ratios in both sexes at all doses. Focal acute gastritis occurred in some rats of both sexes at all doses and this effect was inversely related to dose. A LOAEL of 40 mg/kg/day (the lowest dose tested) is identified in this study.

- Colley et al. (1983) administered technical-grade chlorothalonil in the diet to Charles River rats (27 males and 28 females per dose) for 13 weeks at concentrations of 0, 1.5, 3.0, 10 or 40 mg/kg/day. Histopathological examination revealed that at a dose of 3.0 mg/kg/day or greater, all males displayed an increased number of irregular intracytoplasmic inclusion bodies in the renal proximal convoluted tubules. A NOAEL of 1.5 mg/kg/day is identified in this study.

- Shults et al. (1983) administered technical chlorothalonil (98.4%) to Charles River CD-1 mice (15/sex/dose) for 90 days at dietary concentrations of 0, 7.5, 15, 50, 275 or 750 ppm (males: 0, 1.2, 2.5, 8.5, 47.7 or 123.6 mg/kg/day; and females: 0, 1.4, 3.0, 9.8, 51.4 or 141.2 mg/kg/day). No treatment-related effects were noted on survival, physical condition, body weight, food consumption or gross pathology. At 750 ppm (141 mg/kg/day), an increase in alkaline phosphatase levels was observed in females only. Increased kidney weight was reported in males dosed at 750 ppm (124 mg/kg/day) and in females dosed at 275 and 750 ppm (51.0 and 141 mg/kg/day). Histopathologically, dose-related changes in the forestomach of mice were characterized by hyperplasia and hyperkeratosis of squamous epithelial cells. These changes were observed in the 50-, 275- and [illegible]-ppm dose groups. No other treatment-related histopathological changes were reported. A NOAEL of 15 ppm (2.5 mg/kg/day) is identified for this study.

- Paynter and Murphy (1967) administered DAC 2787 (chlorothalonil) to beagle dogs (4/sex/dose) for 16 weeks at dietary concentrations of 0, 250, 500 or 750 ppm (approximately to 0, 6.3. 12.5 or 18.8 mg/kg/day; Lehman, 1959). No effects attributable to chlorothalonil were noted in terms of appearance, behavior, appetite, elimination, body weight changes, gross pathology or organ weights. Hematological, biochemical and urinalysis values were generally within accepted limits in treated and control animals, except for slightly elevated protein-bound iodine values in treated dogs (especially high-dose females). No compound-related histopathology was noted. Based on this, a NOAEL of 750 ppm (18.8 mg/kg/day) is identified.

- Hastings et al. (1975) administered chlorothalonil to Wistar albino rats (15/sex/dose for treatment groups, 30/sex for controls) for four months at dietary concentrations of 0, 1, 2, 4, 15, 30, 60 or 120 ppm (approximately 0, 0.05, 0.1, 0.2, 0.8, 1.5, 3 or 6 mg/kg/day; Lehman, 1959). No significant differences between treated and control groups were seen in body weight, food consumption, mortality or gross pathological changes. Histopathological examination of the kidneys revealed no demonstrable effects at any dose level. A NOAEL of 120 ppm (6 mg/kg/day) is identified.

- Blackmore et al. (1968) administered DAC 2787 (chlorothalonil) to Charles River rats (35/sex/dose) for 22 weeks at dietary concentrations of 0, 250, 500, 750 or 1,500 ppm (approximately 0, 12.5, 25, 37.5 or 75 mg/kg/day; Lehman, 1959). At all dose levels, male rats gained less weight from weeks 11 to 22. Females gained less weight from weeks 9 to 22 at 750 and 1,500 ppm (37.5 or 75 mg/kg/day). Food consumption values were similar for all groups. No differences between control and test animals were reported for various hematological parameters, urinalysis and plasma and urine electrolytes. Results of gross necropsy revealed that livers and kidneys of males treated at 750 or 1,500 ppm (37.5 or 75 mg/kg/day) were larger than controls. Microscopic examinations demonstrated dose-related compound-induced alterations in the kidneys of both sexes at all doses. These changes were characterized by irregular swelling of the tubular epithelium, epithelial degeneration and tubular dilatation. There was a significant increase in renal tubular diameter in males at all dose levels. Accordingly, a LOAEL of 250 ppm (12.5 mg/kg/day) is identified.

- Blackmore and Kundzin (1969) administered technical-grade DAC 2787 (chlorothalonil), assumed by authors to be 100%, to rats (strain not specified) (35/sex/dose) for 1 year at dietary concentrations of 0, 4, 10, 20, 30, 40 or 60 ppm. The authors indicated that these dietary levels correspond to 0, 0.2, 0.5, 1.0, 1.5, 2.0 or 3.0 mg/kg/day. No compound-related effects on physical appearance, behavior, growth, food consumption, survival, clinical laboratory values, organ weights or gross pathology were noted. Microscopically, there were kidney alterations in both sexes at 40 and 60 ppm (2.0 and 3.0 mg/kg/day). These alterations occurred primarily in the deeper cortical tubules and consisted of increased vacuolation of epithelial cells accompanied by swelling or hypertrophy of the affected cells, often with the deposition of an eosinophilic droplet material in the cytoplasm of the vacuole. Statistical significance was not addressed. A NOAEL of 30 ppm (1.5 mg/kg/day) is identified.

- Holsing and Voelker (1970) administered technical chlorothalonil, assumed by authors to be 100%, to beagle dogs (eight/sex/dose) for 104 weeks at dietary concentrations of 0, 60 or 120 ppm (approximately 0, 1.5 or 3 mg/kg/day; Lehman, 1959). After 2 years of administration, compound-related histopathological changes were observed in the kidneys of males fed 120 ppm (3 mg/kg/day). Males fed 60 ppm (1.5 mg/kg/day) and females fed both dose levels were comparable to controls. The observed changes included increased vacuolation of the epithelium in both the convoluted and collecting tubules and increased pigment in the convoluted tubular epithelium. Clinical findings, terminal body weight, organ-to-body weight ratios and gross pathology revealed no conclusive compound-related trends. A NOAEL of 60 ppm (1.5 mg/kg/day) is identified.

- Tierney et al. (1983) administered technical grade chlorothalonil (97.7% pure) to Charles River CD-1 mice (60/sex/dose) for 2 years at dietary concentrations of 0, 750, 1,500 or 3,000 ppm. The authors indicated that these dietary levels were approximately 0, 119.4, 251.1 or 517.4 mg/kg/day for males and 0, 133.6, 278.5 or 585.0 mg/kg/day for females. No treatment-related effects on body weight, food consumption, physical condition or hematological parameters were noted. A slightly increased mortality rate was noted in males receiving 3,000 ppm (517.4 mg/kg/day). Also, kidney-to-body weight ratios and kidney-to-brain weight ratios were increased significantly in all test groups. Gross necropsy revealed a number of renal effects including kidney enlargement, discoloration, surface irregularities, pelvic dilation, cysts, nodules and masses. Effects on the stomach included an increased incidence in masses or nodules. In the stomach and esophagus, nonneoplastic histopathological effects were noted at all dose levels, and included hyperplasia and hyperkeratosis of the squamous mucosa. This was considered to be indicative of mucosal irritation. Other changes in the stomach included mucosal and submucosal inflammation, focal necrosis or ulcers of mucosa and hyperplasia of glandular mucosa. Reported histopathological effects on the kidney included an increase in the incidence and severity of glomerulonephritis, cortical tubular degeneration and cortical cysts. These changes were not dose-related, but they did occur at higher incidences in treated animals. Based on the information presented in this study, a LOAEL of 750 ppm (119.4 mg/kg/day-males; 133.6 mg/kg/day-females) is identified.

Reproductive Effects

- In a three-generation reproduction study, Paynter and Kundzin (1967) administered a mixture containing 93.6% chlorothalonil to Charles River rats (10 males and 20 females per dose) at dietary concentrations of 0 or 5,000 ppm (approximately 0 or 250 mg/kg/day; Lehman, 1959). At the dose tested, the test material produced significant growth suppression in the nursing litters of each generation. Reproductive performance was not affected and pups showed no malformations attributable to the test substance. Body weight gains for exposed male and female rats of each generation were lower than controls.

Developmental Effects

- Rodwell et al. (1983) administered technical chlorothalonil (98% pure) by gavage, in aqueous methylcellulose, at doses of 0, 25, 100 or 400 mg/kg/day to Sprague-Dawley Cobs CD rats (25/dose level) on days 6 to 15 of gestation. No compound-related external, internal or skeletal malformations were observed in fetuses. At 400 mg/kg/day, maternal toxicity was noted (as evidenced by changes in appearance, three deaths, decreased body weight gain and food consumption). A slight increase in the number of early embryonic deaths was associated with this maternal toxicity. This study identifies a NOAEL of 400 mg/kg/day for teratogenic effects and a NOAEL of 100 mg/kg/day for maternal toxicity.

- Shirasu and Teramoto (1975) administered chlorothalonil (99.3% pure) by gavage to Japanese white rabbits (eight controls, nine per dose) at doses of 0, 5 or 50 mg/kg/day on days 6 to 18 of gestation. At 50 mg/kg/day, four of the nine does aborted. No compound-related growth retardation or malformations were noted in offspring in any test group. This study identifies a NOAEL of 50 mg/kg/day for teratogenic effects and a NOAEL of 5 mg/kg/day for maternal toxicity.

Mutagenicity

- Quinto et al. (1981) reported that chlorothalonil (purity and concentrations were not specified) was not mutagenic, with or without metabolic activation, in five tester strains of *Salmonella typhimurium*.

- Wei (1982) reported that chlorothalonil (90% pure), at concentrations up to 764 ug/plate, was not mutagenic in *S. typhimurium* strains TA 1535, 1537, 1538, 100 or 98, with or without liver or kidney activation systems.

- Kouri et al. (1977c) reported that DTX-77-0035 (97.8% chlorothalonil) at concentrations up to 6.6 ug/plate did not induce point mutations in *S. typhimurium* strains TA 1535, 100, 1537, 1538 or 98, with or without S-9 activation.

- Shirasu et al. (1975) reported the results of a reverse mutation test using *S. typhimurium* strains TA 1535, 1537, 1538, 98 and 100 and *Escherichia coli* WP2 hcr^{+} and WP2 hcr^{-}. Chlorothalonil (99.3%) failed to produce an effect without activation at concentrations up to 500 pg/plate; negative results also were obtained with activation at chlorothalonil concentrations up to 100 pg/plate.

- Kouri et al. (1977b) reported the effects of DTX-77-0033 (97.8% chlorothalonil) in a DNA repair assay using *S. typhimurium* strains TA 1978 and 1538. Chlorothalonil, dissolved in dimethylsulfoxide at 1 mg/mL and tested at 2, 10 and 20 uL of the stock solution per plate, was found to be active in both strains with or without metabolic activation.

- DeBertoldi et al. (1978) reported that a commercial preparation of chlorothalonil (2,500 ppm of active ingredient) did not induce mitotic gene conversions in *Saccharomyces cerevisiae* in the presence or absence of metabolic activation systems. In tests on *Aspergillus nidulans* using both resting and germinating conidia, chlorothalonil (up to 200 ppm) did not induce mitotic gene conversions.

- Shirasu et al. (1975) reported that, at concentrations up to 200 ug/disk, chlorothalonil (99.3%) was negative in a rec-assay using *Bacillus subtilis* strains H17 and M45.

- Kouri et al. (1977a) exposed Chinese hamster cells (V-79) and mouse fibroblast cells (BALB/3T3) *in vitro* to DTX-77-0034 (chlorothalonil, 97.8% pure) at concentrations of 0.3 ug/mL (for V-79 cells) or 0.03 ug/mL (for mouse fibroblast cells). The V-79 cells were tested without metabolic activation; the BALB/3T3 cells were tested with and without metabolic activation. Chlorothalonil was not mutagenic in either cell type.

- Mizens et al. (1983a) reported the results of a micronucleus test in Wistar rats, Swiss CFLP mice and Chinese hamsters. Rats were dosed at 0, 8, 40, 200, 1,000 or 5,000 mg/kg; mice and hamsters received 0, 4, 20, 100, 500 or 2,500 mg/kg. All animals were dosed by gavage and all received two doses, 24 hours apart. Technical chlorothalonil (98.2% ai) did not induce bone marrow erythrocyte micronuclei in any of the species tested.

- Legator (1974) reported the results of an in vivo cytogenetic test on DAC-2787 (chlorothalonil, more than 99% pure) in mice (strain not specified) using the micronuclei procedure. The test compound was administered by gavage for 5 days at a concentration of 6.5 mg/kg/day. At this concentration, chlorothalonil did not increase the number of cells with micronuclei.

- Legator (1974) presented the results of a host-mediated assay using male Swiss albino mice and S. typhimurium strains G-46, TA1530, C-207, TA1531, C-3076, TA1700, D-3056 and TA1724. Mice (10/dose) received DAC-2787 (chlorothalonil, 99% pure) by gavage for 5 days at 6.5 mg/kg/day. The compound did not produce any measurable mutagenic response when initially evaluated in vitro against the eight tester strains of S. typhimurium. When the tester strains were inoculated into treated mice, no increase in mutation frequency was observed.

- Legator (1974) presented the results of a dominant lethal assay in which male mice (strain not specified) were dosed with DAC-2787 (chlorothalonil, 99% pure) for five days at 6.5 mg/kg/day. These mice were mated with untreated females, and the number of early fetal deaths and preimplantation losses were measured. There was no significant difference in the fertility rates between test and control animals during weeks 1 to 7. At week 8, there was a significant decrease in fertility in the test group.

- Mizens et al. (1983b) presented the results of a chromosomal aberration test in Chinese hamsters. The test animals received two doses of technical chlorothalonil, 24 hours apart, by gavage at concentrations of 0, 8, 40, 200, 1,000 or 5,000 mg/kg. At 5,000 mg/kg, a statistically significant increase in bone marrow chromosomal abnormalities was observed. However, the authors concluded that this effect could not be attributed to chlorothalonil (98.2% ai) because the animals exhibited toxic responses to dosing.

Carcinogenicity

- NCI (1980) reported the results of a study in which technical-grade chlorothalonil (98.5%) was administered to Osborne-Mendel rats (50/sex/dose) for 80 weeks at Time-Weighted Average (TWA) dietary doses for both males and females of 5,063 or 10,126 ppm, respectively. These dietary doses have been calculated to correspond to approximately 253 and 506 mg/kg/day (Lehman, 1959). Matched controls consisted of groups of 10 untreated rats of each sex; pooled controls consisted of the matched controls combined with 55 untreated male or female rats from other bioassays. An observation period of 30 to 31 weeks followed dosing. Clinical signs that appeared with increased frequency in dosed rats included hematuria and, from week 72 on, bright yellow urine. Adenomas and carcinomas of renal tubular epithelium occurred with a significant ($p = 0.03$, males; $p = 0.007$, females) dose-related trend. The frequency of renal tumors was statistically greater in the high-dose males ($p = 0.035$) and high-dose females ($p = 0.016$) than in corresponding controls (males: pooled controls, 0/62; low dose, 3/46; high dose, 4/49; females: pooled controls, 0/62; low dose, 1/48; high dose, 5/50). The observed adenomas and carcinomas were considered to be histogenically related. Results of this study were interpreted as sufficient evidence of carcinogenicity in Osborne-Mendel rats.

° NCI (1980) also reported a study in which technical-grade chlorothalonil (98.5%) was administered to B6C3F1 mice (50/sex/dose) for 80 weeks at TWA dietary doses of 2,688 or 5,375 ppm for males and 3,000 or 6,000 ppm for females. These dietary doses have been calculated to correspond to approximately 403.2 or 806.3 mg/kg for males and 450 or 900 mg/kg for females (Lehman, 1959). Matched controls consisted of 10 untreated mice of each sex; pooled controls consisted of the matched controls combined with 50 untreated male or female mice from other bioassays. An observation period of 11 to 12 weeks followed dosing. Since the dosed female mice did not show depression in mean body weights or decreased survival compared with the controls, they may have been able to tolerate a higher dose. No tumors were found to occur at a greater incidence among dosed animals than among controls. It was concluded that, under the conditions of this bioassay, chlorothalonil was not carcinogenic in $B6C3F_1$ mice.

° Tierney et al. (1983) administered technical-grade chlorothalonil (97.7% pure) to Charles River CD-1 mice (60/sex/control and dose groups) for 2 years at dietary concentrations of 0, 750, 1,500 or 3,000 ppm. The authors indicated that these dietary levels were equivalent to 0, 119, 251 or 517 mg/kg/day for males and 0, 133, 278 or 585 mg/kg/day for females. Increased incidences of squamous cell tumors of the forestomach were noted in all treatment groups. These tumors consisted principally of carcinomas, although papillomas were also seen. This increased incidence was statistically significant in females dosed at 1,500 ppm (279 mg/kg/day). No clear dose-related trend in the incidence of these tumors was observed. A slight increase in the incidence of tumors of the glandular epithelium of the fundic stomach was observed in dosed animals; this increase was neither statistically significant nor dose-related. When the numbers of animals with epithelial tumors of the fundic or forestomach were combined, the incidence of these tumors showed a statistically significant increase in the 1,500- and 3,000-ppm female dose groups (279 and 585 mg/kg/day). No treatment-related renal neoplasms were seen in any female dose group. Increased incidences of adenomas and carcinomas in renal cortical tubules were noted in all treated groups of male mice. These changes did not show a dose-response relationship; the increased incidence was statistically significant only in the 750 ppm (251 mg/kg/day) group. The authors concluded that the administration of chlorothalonil caused an increase in the incidence of primary gastric tumors and, in male mice only, caused an increase in the incidence of renal tubular neoplasms.

- Wilson et al. (1985) gave technical chlorothalonil (98.1% pure with less than 0.03% hexachlorobenzene) to Fischer 344 rats (60/sex/dose) in their diet at dose levels of 0, 40, 80 or 175 mg/kg/day. Males were treated for 116 weeks, while females received the chemical for 129 weeks. Survival among the various groups was comparable. In both sexes, at the high-dose level, there were significant decreases in body weights. In addition, there were also significant increases in blood urea nitrogen and creatinine, while there were decreases in serum glucose and albumin levels. In both sexes, there were dose-dependent increases in kidney carcinomas and adenomas at doses above 40 mg/kg/day. In the high-dose females, there was also a significant increase in stomach papillomas. The data show that, in the Fischer 344 rat, chlorothalonil is a carcinogen.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination [illegible] a One-day HA for chlorothalonil. Accordingly, it is recommended that [illegible] Longer-term HA value (200 ug/L, calculated below) for a 10-kg child be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

No information was found in the available literature that was suitable for determination of a Ten-day HA for chlorothalonil. Accordingly, it is recommended that the Longer-term HA value (200 ug/L, calculated below) for a 10-kg child be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The studies by Colley et al. (1983), Blackmore and Kundzin (1969) and Blackmore and Shott (1968) have been selected to serve as the basis for the Longer-term HA for chlorothalonil. In the study by Colley et al., technical-grade chlorothalonil was administered in the diet to Charles River rats for 13 weeks at concentrations of 0, 1.5, 3.0, 10 or 40 mg/kg/day. Histopathological examinations revealed that at doses of 3.0 mg/kg/day or greater, male rats displayed an increased number of intracytoplasmic inclusion bodies in the proximal convoluted renal tubules. Blackmore and Shott (1968), gave technical-grade chlorothalonil in the diet to Charles River rats for 90 days at doses of 0, 0.2, 0.5, 1.0, 1.5, 2.0 or 3.0 mg/kg/day. At the two highest dose levels, the kidneys exhibited occasional vacuolation and swelling of the epithelial cells lining the deeper proximal convoluted tubules. In the Blackmore and Kundzin (1969) study, technical-grade chlorothalonil was administered in the diet to rats for 1 year at doses of 0, 0.2, 0.5, 1.0, 1.5, 2.0 or 3.0 mg/kg/day. At the 2 higher doses, there were alterations in the deeper convoluted renal tubules in both sexes. Each of the studies identified a NOAEL of 1.5 mg/kg/day.

The Longer-term HA for a 10 kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.5\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.15\ \text{mg/L}\ (200\ \text{ug/L})$$

where:

1.5 mg/kg/day = NOAEL, based on absence of kidney effects in rats exposed to chlorothalonil in the diet for 13 weeks.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.5\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 0.525\ \text{mg/L}\ (500\ \text{ug/L})$$

where:

1.5 mg/kg/day = NOAEL, based on absence of kidney effects in rats exposed to chlorothalonil in the diet for 13 weeks.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Holsing and Voelker (1970) has been selected to serve as the basis for the Lifetime HA for chlorothalonil. In this study, technical-grade chlorothalonil was administered to beagle dogs (eight/sex/dose) for 104 weeks at dietary concentrations of 0, 60 or 120 ppm (0, 1.5 or 3.0 mg/kg/day). The results following 2 years of administration revealed compound-related histopathological changes in the kidneys of males fed 120 ppm (3 mg/kg/day). Males fed 60 ppm (1.5 mg/kg/day) and females fed both dose levels were comparable to controls. The observed changes included increased vacuolation of the epithelium in both the convoluted and collecting tubules and increased pigment in the convoluted tubule epithelium. From these results, a NOAEL of 1.5 mg/kg was identified.

Using this NOAEL, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(1.5 \text{ mg/kg/day})}{(100)} = 0.015 \text{ mg/kg/day}$$

where:

1.5 mg/kg/day = NOAEL, based on absence of histopathological changes in dogs fed chlorothalonil for one year.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.015\ \text{mg/kg/day})\ (70\ \text{kg})}{2\ \text{L/day}} = 0.525\ \text{mg/L}\ (500\ \text{ug/L})$$

where:

0.015 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Chlorothalonil is classified in Group B2: probable human carcinogen. Accordingly, a Lifetime HA is not recommended for chlorothalonil.

The estimated excess cancer risk associated with lifetime exposure to drinking water containing chlorothalonil at 525 ug/L (the DWEL) is 3.5×10^{-4}. This estimate represents the upper 95% confidence limit from extrapolations prepared by OPP and ODW using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- In an NCI bioassay (1980), technical grade chlorothalonil was administered in the diet at 253 or 506 mg/kg/day to Osborne-Mendel rats for 80 weeks. A statistically significant increase in the frequency of renal tumors was observed in high-dose males and females.
- NCI (1980) reported that chorothalonil was not carcinogenic in $B6C3F_1$ mice when administered in the diet, at 403 or 806 mg/kg and 450 or 900 mg/kg for males and females, respectively, for 80 weeks. However, Tierney et al. (1983) concluded that chlorothalonil was carcinogenic in Charles River CD-1 which received the compound (0, 119, 251 or 517 mg/kg/day for males and 0, 134, 279 or 585 mg/kg/day for females) in the diet for 2 years. Increased incidences of squamous cell papilloma and carcinoma of the forestomach were noted in all treatment groups. This increase was statistically significant only in the mid-dose females. Increased incidences of adenoma and carcinoma of the renal cortical tubules were observed in all treatment groups. Again, no dose-response was noted, since these increases were statistically significant only in the mid-dose males.

- The International Agency for Research on Cancer (IARC, 1983) has evaluated the carcinogenic potential of chlorothalonil and concluded that there is limited evidence of carcinogenicity in experimental animals.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), chlorothalonil is classified in Group B2: probable human carcinogen. This category is for chemicals for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

- From the Wilson et al. (1985) data, OPP calculated a q_1* of 2.4 x 10^{-2} (mg/kg/day)$^{-1}$. The 95% upper limit lifetime dose in drinking water associated with a 10^{-6} excess risk level is 1.5 ug/L. Corresponding levels for 10^{-5} and 10^{-4} are 15 and 150 ug/L, respectively. While recognized as statistically alternative approaches, the range of risks described by using any of these modelling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the Agency has recommended use of the linearized multistage approach However, for completeness, the 10^{-6} risk numbers for other models will be given. These values, at the 10^{-6} level, are: multihit - 9 ug/L; one hit - 2 ug/L; probit - 51 ug/L; logit - 0.8 ug/L; and Weibel - 0.6 ug/L.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- WHO Temporary Acceptable Daily Intake = 0.005 mg/kg/day (Vettorazzi and Van den Hurk, 1985).

- EPA/OPP has calculated a PADI of 0.015 mg/kg/day based on the NOAEL of 1.5 mg/kg/day identified in the 2-year dog study (Holsing and and Voelker, 1970) and an uncertainty factor of 100 (U.S. EPA, 1984a).

- U.S. EPA established tolerances in or on raw agricultural commodities residue levels of 0.1 to 5 ppm (40 CFR 180.275, 1985).

VII. ANALYTICAL METHODS

- Analysis of chlorothalonil is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using an electron capture detector. This method has been validated in a single laboratory, and estimated detection limits have been determined for analytes in this method, including chlorothalonil. The estimated detection limit for chlorothalonil is 0.025 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Reverse osmosis (RO) is a promising treatment method for pesticide-contaminated water. As a general rule, organic compounds with molecular weights greater than 100 are candidates for removal by RO. Larson et al. (1982) reported 99% removal efficiency of chlorinated pesticides by a thin-film composite polyamide membrane operating at a maximum pressure of 1,000 psi and a maximum temperature of 113°F. More operational data are required, however, to specifically determine the effectiveness and feasibility of applying RO for the removal of chlorothalonil from water. Also, membrane adsorption must be considered when evaluating RO performance in the treatment of chlorothalonil-contaminated drinking water supplies.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

CYANAZINE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

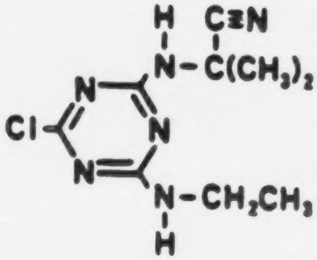
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 21725-46-2

Structural Formula



2-[[4-Chloro-6-(ethylamino)-1,3,5-triazin-2-yl]amino]-2-methylpropanenitrile

Synonyms

- Cyanazine (common name), Bladex, Fortrol, Payze, SD1518, VL19804, DW3418 and WL19805 (Meister, 1983).

Uses

- Cyanazine is used as a pre- and postemergence herbicide for the control of annual grasses and broad leaf weeds (U.S. EPA, 1984a).

Properties (U.S. EPA, 1984a; Meister, 1983; CHEMLAB, 1985)

Chemical Formula	$C_9H_{13}ClN_6$
Molecular Weight	240.7
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	167.5 to 169°C
Density	0.35 (fluffed) to 0.45 (packed) g/cc
Vapor Pressure (20°C)	1.6×10^{-9} to 7.5×10^{-9} mm Hg
Water Solubility (25°C)	171 mg/L
Log Octanol/Water Partition Coefficient	2.24
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Cyanazine has been found in 1,708 of 5,297 surface water samples analyzed and in 21 of 1,821 ground water samples (STORET, 1988). Samples were collected at 392 surface water locations and 1,314 ground water locations. The 85th percentile of all non-zero samples was 4.11 ug/L in surface water and 0.20 ug/L in ground water sources.

The maximum concentration found in surface water was 1,300 ug/L and in ground water it was 3,500 ug/L. Cyanazine was found in surface water in 7 States and in ground water in 5 States. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Cyanazine was identified in drinking water in New Orleans, Louisiana, in concentrations ranging from 0.01 to 0.35 ug/L.

- Cyanazine was monitored in a newly-built reservoir on the Des Moines River in Iowa during September 1977 through November 1978. Agricultural runoff (from corn and soybeans) was a major source of pollution in the river: levels of 71 to 457 ng/L were detected during the active months of May through August; levels of 2 to 151 ng/L were detected during September through December; and zero levels were found from January through April (U.S. EPA, 1984a; NAS, 1977).

- Cyanazine has been found in surface water in Ohio river basins (Datta, 1984).

- Cyanazine has also been found in ground water in Iowa and Pennsylvania; typical positives found were 0.1 to 1.0 ppb (Cohen et al., 1986).

Environmental Fate

- 14C-Cyanazine, at 5 to 10 ppm, degraded with a half-life of 2 to 4 weeks in an air-dried sandy clay loam soil, 7 to 10 weeks in a sandy loam soil, 10 to 14 weeks in a clay soil, and 9 weeks in a fresh sandy clay soil incubated in the dark at 22°C and field capacity (Osgerby et al., 1968). Three degradation products, the amide and two acids, were identified in all four soils; a fourth degradate, the amine, was found only in the air-dried sandy clay loam soil.

- Freundlich K values were 0.72 for a sandy loam soil (2.0% organic matter), 2.0 for a sandy clay soil (5.4% organic matter), 1.25 for a sandy clay loam soil (6.8% organic matter) and 6.8 for a clay soil (16% organic matter) treated with unaged ^{14}C-cyanazine (Osgerby et al., 1968). No linear correlation was found between organic matter content and adsorption.

- 14C-Cyanazine readily moved through columns of sandy clay loam (52% of applied compound) and loamy sand (18% of applied) soil leached with 78 cm of water over a 13-day period; unaged ^{14}C-cyanazine was intermediately mobile on sandy clay loam and of low mobility on loamy sand soil thin-layer chromatography (TLC) plates (R_f 0.36 and 0.20, respectively) (McMinn and Standen, 1981). Aerobically and anaerobically aged ^{14}C-cyanazine residues, primarily the amide degradate (SD 20258), were intermediately mobile to mobile on sandy clay loam soil TLC plates.

- ° Aged ^{14}C-cyanazine residues readily leached through columns containing sand (47.8% of applied compound), loamy sand (69.7% of applied compound) and sandy loam (26.9% of applied compound) soils eluted with 20 cm of water (Eadsforth, 1984). The amide degradation product (SD 20258) was predominant in the leachate from the sandy soil (45% of radioactivity in leachate); the acid degradate (SD 20196) was predominant in leachate from the loamy sand (84%) and sandy loam (47%) soils. Unaltered cyanazine and SD 31222 were also identified in leachate from all three soils ($\leq$6% of recovered residues).

III. PHARMACOKINETICS

Absorption

- ° Studies by Shell Chemical Company (1969) and Hutson et al. (1970) indicated that cyanazine is rapidly absorbed from the gastrointestinal tract when administered orally at low dosage levels to three different animal species: rat, dog and cow. Measurements of urinary, fecal and biliary excretion indicated that 80 to 88% of 2,4,6-^{14}C-labeled cyanazine was eliminated within 4 days from the rat and dog, and within 21 days from the cow. The initial dosages were 1 to 4 mg/kg for the rat, 0.8 mg/animal for the dog and 5 ppm in the total ration of the cow. The dosages were administered by gavage in the rat studies and in gelatin capsules in the dog study.

Distribution

- ° In rats treated with a single oral dose of 4 mg/kg cyanazine, samples of the carcass, skin and gut reflected 2.02, 0.62 and 2.73% residual radioactivity, respectively, 4 days after exposure (Shell, 1969).

- ° In cows, samples of brain, liver, kidney, muscle and fat reflected concentrations of 0.55, 0.27, 0.24, 0.14 to 0.06 and less than 0.06 ppm cyanazine, respectively, after 21 days of continuous exposure to feed that contained 5 ppm cyanazine; however, when a lower dosage (0.2 ppm) was used in the feed, the detectable residues in each of these tissues were less than 0.05 ppm (Shell, 1969).

Metabolism

- ° Based on the analyses of metabolites in urine, the major metabolic pathways of cyanazine in the rat and cow involved: (1) conversion of the cyano group to an amide to form 2-chloro-4-ethylamino-6-(1-amido-1-methylethylamino)-s-thiazine; (2) N-deethylation to form 2-chloro-4-amino-6-(1-cyano1-methyl-ethylamino)-s-triazine; (3) conversion of the cyano group of deethylate cyanazine to form the amide of deethylated cyanazine, 2-chloro-4-amino-6(1-amino-1-methylethylamino)-s-triazine; (4) dechlorination via glutathione, partial hydrolysis of glutathione conjugate and N-acetylation to form mercapturic acid, N-acetyl-S-[4-amino-6-(1-cyano-1-methylethylamino) L-cysteine; and (5) dechlorination via hydrolysis (occurs only in the cow) to form

2-hydroxy-4-ethylamino-6-(1-carboxy-1-methylethylamino)-s-triazine and 2-hydroxy-4-amino-6-(1,carboxy-1-methylamino)-s-triazine, respectively (Shell, 1969).

- Studies by Shell Chemical Company (1969) and Hutson et al. (1970) in rats with ring-labeled and side-chain-labeled cyanazine (cyano-^{14}C, isopropyl-^{14}C and ethylamino-^{14}C) indicated that only the ethylamino-^{14}C side chain underwent extensive degradation, since 47% of the initial radioactivity was detected in the exhaled carbon dioxide. Thus, N-deethylation was found to be a major route of degradation of cyanazine.

- Crayford and Hutson (1972) identified 5 metabolites in urine of rats, an additional 2 (total 7) in feces and 4 metabolites in bile.

- Crayford et al. (1970) studied the metabolism of two major plant metabolites, DW4385 and DW4394, in rats. These two compounds were identified in the rat metabolism studies by Crayford and Hutson (1972) as 2-hydroxy-4-ethylamino-6-(1-carboxy-1-methylamino)-s-triazine (DW4385) and as 2-hydroxy-4-amino-6-(1-carboxy-1-methylethylamino)-s-triazine) (DW4394). Approximately 91% of compound DW4385 and 84% of compound DW4394 were recovered unchanged from urine and feces.

Excretion

- Orally administered low doses of cyanazine (described above) were rapidly excreted in the urine and feces of rats and dogs (Shell, 1969; Hutson et al., 1970; Crayford and Hutson, 1972).

- In rats treated with 1 to 4 mg/kg cyanazine by gavage, a total of 88% of cyanazine was eliminated in 4 days. Elimination via urine was almost equal to elimination via feces; about 5.37% of the administered cyanazine remained in the body; and approximately 21% of the 1 mg/kg dose appeared in the bile within the first 20 hours (Shell, 1969).

- Hutson et al. (1970) reported that 33% of an oral dose of cyanazine was excreted in the urine of rats within 24 hours.

- A study in rats with ^{14}C-labeled 4-ethyl-amino cyanazine indicated that 47% of the radioactivity was eliminated in carbon dioxide (Shell, 1969).

- In dogs administered 0.8 mg of cyanazine in gelatin capsules, 51.67 and 36.29% of the dose were eliminated in the urine and feces, respectively, over a 4-day period (Shell, 1969).

- In cows exposed to treated feed (5 ppm cyanazine) for 21 consecutive days, the amount of daily excretion of radioactivity in urine and feces was constant throughout the study period. The total cyanazine equivalents in urine and feces were 53.7 and 26.8% of the dose, respectively. The concentration in milk was reported as 0.022 ppm (Shell, 1969).

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of cyanazine in humans.

Animals

Short-term Exposure

- Acute oral LD_{50} values reported for rats range from 149 to 835 mg/kg (SRI, 1967b; NIOSH, 1987; Young and Adamik, 1979b; Meister, 1983). In these studies, the percentage of active ingredient (a.i.) in the tested product(s) was not clearly identified. However, studies by Walker et al. (1974) with technical cyanazine (97% a.i.) in three different animal species reflected LD_{50}s of 182, 380 and 141 mg/kg for the rat, mouse and rabbit, respectively.

- The acute dermal LD_{50} in rabbits treated with technical cyanazine (purity unspecified) was >2,000 mg/kg (SRI, 1967a; Young and Adamik, 1979c); in rats, the LD_{50} was >1,200 mg/kg (97% a.i.) (Walker et al., 1974).

- The acute inhalation LC_{50} for cyanazine dust (% a.i. not specified) in rats was >2.28 mg/L/hr (Bishop, 1976) (thus cyanazine would be classified in toxicity category III).

- In a study by Walker et al. (1968), groups of 10 female CFE rats, 5 months old, were treated by gavage with single oral doses of 1, 5 or 25 mg/kg of a wettable powder formulation (75% a.i.); the control group received water. No diuretic effects were produced in the rats receiving the formulation; however, serum protein and potassium concentrations increased at the high dose, and serum osmolality increased at 5 mg/kg, the Lowest-Observed-Adverse-Effect Level (LOAEL). The No-Observed-Adverse-Effect Level (NOAEL) in this study appeared to be 1 mg/kg; however, this study did not provide enough information to determine the presence or absence of more significant effects at this dosage level.

- A 4-week oral toxicity study by Walker et al. (1968) was performed using groups of 10 male and 10 female CFE rats, 5 weeks of age, receiving diets containing 1, 10 or 100 ppm cyanazine (75% or 97% a.i.) for 4 weeks; These doses are equivalent to 0.05, 0.5 or 5 mg/kg/day (Lehman, 1959). A control group of 20 animals/sex was used. After 4 weeks, urine samples were collected for 16 hours (overnight), and blood samples were used to determine the kidney function. Reductions in body weight and food intake were noted at the high-dose level. Osmolal clearance decreased in males, and this change was associated with a decrease in free water clearance in both the low- and mid-dose groups. In females, decreased urine and increased serum osmolality were observed in the mid-dose group, and both creatinine clearance and urine potassium concentrations increased in the low-dose group.

The LOAEL in this study appeared to be 0.05 mg/kg/day (lowest dose tested) based on kidney function tests, although additional information was not available to determine if any other significant adverse effects were noted at this level.

Dermal/Ocular Effects

- Cyanazine caused mild eye irritation at 100 mg (Young and Adamik, 1979a) and slight skin irritation at 2,000 mg (Young and Adamik, 1979c) in rabbits. A skin sensitization test in guinea pigs was negative (Walker et al., 1974; Young and Adamik, 1979d).

Long-term Exposure

- In a 13-week oral study in dogs (Walker and Stevenson, 1968a; Walker et al., 1974), groups of 5- to 7-month old beagle dogs, four animals/sex/treatment group, were given daily doses of 1.5, 5 or 15 mg/kg/day cyanazine in gelatin capsules. A control group of five animals/sex was given empty capsules. The test material caused emesis within the first hour of dosing in all of the high-dose males. Reduced body weight gain was also noted in the high-dose group during the second half of the study period as well as increased kidney and liver weights in the females of this group. Thus, the LOAEL was 15 mg/kg/day and the NOAEL was 5 mg/kg/day.

- In a 13-week mouse feeding study (Fish et al., 1979), groups of 12 animals/sex/dose were fed diets containing 10, 50, 500, 1,000 or 1,500 ppm, equivalent to 1.5, 7.5, 75, 150 or 225 mg/kg/day (Lehman, 1959). The control group consisted of 24 animals/sex. Body weight gain reduction was observed in both sexes at 75 mg/kg/day and above. Statistically significant increases in liver weights were observed in both sexes at 75 mg/kg/day and above. Thus, the LOAEL was 75 mg/kg/day and the NOAEL was 7.5 mg/kg/day.

- An initial 13-week rat feeding study by Walker et al. (1968) was performed using 0.1, 1.0 or 100 ppm (equivalent to 0.005, 0.05 or 0.5 mg/kg/day; Lehman, 1959) of technical cyanazine (purity not specified: 97% or 75% a.i.) in feed. Each dosage group had 20 animals/sex; the control group had 40 animals/sex. Body weight gain decreased in all dosage groups in males and in the high-dose female group. A NOAEL was not reflected in this study for males, although it appeared to be 0.05 mg/kg/day for females.

- Walker and Stevenson (1968b) repeated the above study in rats at dose levels of 1.5, 3, 6, 12, 25, 50 or 100 ppm; these levels are equivalent to 0.075, 0.15, 0.30, 1.25, 2.5 or 5 mg/kg/day (Lehman, 1959). Similar effects were noted; however, a NOAEL of 25 ppm (1.25 mg/kg/day) was identified.

- In a 2-year study in dogs (Walker et al., 1970a), groups of 4- to 6-month-old beagle dogs were treated with technical cyanazine (97% a.i., in gelatin capsules) at dose levels of 0.625, 1.25 or 5 mg/kg/day. Each group consisted of four animals/sex. The control group consisted of six animals/sex and received empty gelatin capsules. Frequent emesis within 1 hour of dosing was observed throughout the study period in the high-dose group; this effect was associated with reduction of growth rate and serum protein. The NOAEL appeared to be 1.25 mg/kg/day; however, this NOAEL should be considered with reservations because the study did not provide adequate explanation relative to missing histological data on one of four female dogs in the 1.25-mg/kg/day dosage group. In addition, the reported data were limited to a summary report.

° In a 2-year study in mice (Shell, 1981), cyanazine technical (purity not specified) was given in feed to CD mice at 10, 25, 50, 250 or 1,000 ppm, equivalent to 1.5, 3.75, 7.5, 37.5 or 150 mg/kg/day (Lehman, 1959); 50 animals/sex were used in the treatment groups, and 100 animals/sex were used as controls. Toxic effects reported at the two high-dose levels, 37.5 and 150 mg/kg/day, included poor appearance and skin sores, increased mortality in the female animals in both groups, increased relative brain weight in both sexes, increased relative liver weight in the two female groups, and decreased absolute and differential leukocyte values in both sexes. Anemia was noted at 150 mg/kg/day in the females, as well as increased blood protein and increased relative kidney weight. Cyanazine did not demonstrate an oncogenic potential in this study. The NOAEL for systemic toxicity in mice appeared to be 50 ppm (7.5 mg/kg/day).

° Two chronic feeding studies in rats were available for review. In one study (Walker et al., 1970b; also cited in Walker et al., 1974), groups of 24 CFE rats/sex/dose received diets containing 6, 12, 25 or 50 ppm, equivalent to 0.3, 0.6, 1.25 or 2.5 mg/kg/day (Lehman, 1959) cyanazine (97% a.i.); 45 rats/sex were used as controls. The authors indicated that no effects due to cyanazine were noted in this study, although reduction in growth rate was noted in both sexes at 2.5 mg/kg/day and in females at 1.25 mg/kg/day. A review of this study (U.S. EPA, 1984b) indicated that cyanazine appeared to be tumorigenic in both male and female rats based on the increased incidences of thyroid tumors in all treatment groups as compared to the study's control group; increased incidences of adrenal tumors also were noted in all male treatment groups. However, this study was considered unacceptable because of several deficiencies: a limited number of tissues per animal were examined microscopically; the tumor incidences were calculated based on the number of animals tested rather than on the number of specific tissues histologically examined; gross examination and histologic findings for nonneoplastic lesions were not adequately reported; and only limited hematology, clinical blood chemistry and urinalyses data were presented.

° Simpson and Dix (1973) repeated the above 2-year study using 1, 3 or 25 ppm, equivalent to 0.05, 0.15 or 1.25 mg/kg/day in the diet of rats (Lehman, 1959); however, convulsions were noted in the rats 3 months after the study initiation and throughout the remainder of the study period. Approximately 42% of the animals were affected, and the incidence was not considered to be dose-related. The incidence of animals with convulsions was similar in both the control and high-dose male groups (21/48 and 11/24, respectively).

- A recent one-year feeding study in dogs using atrazine (98% a.i.) by Dickie (1986) has been evaluated by the Agency. Five experimental groups of 6 animals/sex/group were exposed to the following doses: 0, 10, 25, 100 or 200 ppm. These doses were equivalent to actual consumption of 0, 0.27, 0.68, 3.20 or 6.11 mg/kg/day for males and 0, 0.28, 0.72, 3.02 or 6.39 mg/kg/day for females, respectively. No systemic toxicity was noted at 10 or 25 ppm. However, dose-related decreases in body weight and body weight gains were noted at 100 and 200 ppm, as well as elevated platelet counts, reduced levels of total protein, albumin and calcium in both sexes. At these two high-dose levels, there were also slight but not statistically significant decreases in spleen weights and increases in relative liver weights in females, and increases in liver weights and decreases in testes weights in males. Other noted changes in organ weights(i.e., heart, lung and kidneys) were not considered significant at these dose levels since they were not consistent with changes in the absolute and relative organ weight values. No gross or microscopic findings related to treatment were noted. Thus, in this study, the LOAEL is 3.1 mg/kg/day and the NOAEL is 0.7 mg/kg/day.

Reproductive Effects

- A three-generation reproduction study in Long-Evans rats (Eisenlord et al., 1969) using technical cyanazine (unknown percentage a.i.) at dietary levels of 3, 9, 27 or 81 ppm (0.15, 0.45, 1.35 or 4.05 mg/kg/day based on the dietary assumptions of Lehman, 1959) did not reflect a significant effect on reproduction parameters. The NOAEL in this study appeared to be 1.35 mg/kg/day; the LOAEL was 4.05 mg/kg/day (highest dose tested) based on findings related to reduced body weight gain in parental animals, and increased relative brain weight and decreased relative kidney weight in F_{3b} female weanlings.

- In a repeat two-generation reproduction study in Sprague-Dawley rats (WIL Research Laboratory, 1987), atrazine (100% a.i.) was administered in feed at 0, 25, 75, 150 or 250 ppm. These doses are equivalent to actual food consumption of 0, 1.8, 5.3, 11.1 or 18.5 mg/kg/day, respectively; however, these values changed during lactation to 0, 3.8, 11.2, 23.0 or 37.1 mg/kg/day, respectively. Dose-related decreases in pups' viability and body weights were noted at 75 ppm and above, therefore, the NOAEL for reproduction may be 25 ppm (3.8 mg/kg/day). However, this level, 25 ppm, (equivalent to 1.8 mg/kg/day during non-lactating periods of the study) may be considered as the LOAEL for parental animals due to the noted decreases in body weight and food consumption at this level.

Developmental Effects

- Cyanazine appeared to cause teratogenic effects and developmental toxicity in two animal species, the rabbit and the rat (Bui, 1985b).

- In the rabbit study (Shell Toxicology Laboratory, 1982), 7- to 11-month-old New Zealand White rabbits were orally dosed with cyanazine (98% a.i.) in gelatin capsules at levels of 0, 1, 2 or 4 mg/kg/day on gestation days 6 through 18 (22 dams/dose/group). At 2 and 4 mg/kg/day, maternal toxic effects included anorexia, weight loss, death and abortion. Alterations in skeletal ossification sites, decreased litter size, and increased postimplantation loss were observed at 2 and 4 mg/kg/day. Malformations were also noted at 4 mg/kg/day as demonstrated by anophthalmia/microphthalmia, dilated brain ventricles, domed cranium and thoracoschisis; however, these responses were observed at levels in excess of maternal toxicity. The maternal and developmental toxicity NOAELs were 1 mg/kg/day.

- In a rat study by Lu et al. (1981, 1982), 122-day-old Fischer 344 rats (30 dams/group) were administered cyanazine (98.5% a.i.) by gavage at dose levels of 0, 1.0, 2.5, 10.0 or 25.0 mg/kg/day on gestation days 6 through 15; the dosages were suspended in a 0.2% Methocel emulsion as a vehicle. Maternal body weight reductions during dosing were noted at the 10- and 25-mg/kg/day levels. Diaphragmatic hernia associated with liver protrusion, microphthalmia and anophthalmia were observed at the 25 mg/kg/day dose level. A teratogenic NOAEL could not be determined from this study at 10 mg/kg/day and a maternal toxicity NOAEL at 2.5 mg/kg/day.

- The above study was repeated in the same strain of rats, Fischer 344, by Lochry et al. (1985) in order to further examine the malformations reported in the study by Lu et al. (1981). In this study, the dams (70/dosage group) were 86 days old. Cyanazine (98% a.i.) was administered by gavage in an aqueous suspension of 0.25% (w/v) methyl cellulose at dose levels of 0, 5, 25 or 75 mg/kg/day on days 6 through 15 of gestation. One-half of the dams in each group were selected for Cesarean delivery on day 20 of gestation. The remaining half of the dams in each group were allowed to deliver, and both they and their pups were observed for 21 days before sacrifice. Maternal body weight reductions during dosing were noted in all dosage groups and appeared to be partly associated with lower food intake during the dosing period. Alteration in skeletal ossification sites were also observed in the fetuses at all dose levels. Teratogenic effects were demonstrated at 25 and 75 mg/kg/day as anophthalmia/microphthalmia, dilated brain ventricles and cleft palate in the fetuses, and abnormalities of the diaphragm (associated with liver protrusion) in pups sacrificed at time of weaning. The maternal and developmental toxicity NOAELs were lower than 5 mg/kg/day (lowest dose tested), and the teratogenic NOAEL was 5 mg/kg/day (Bui, 1985a).

- An additional study in Sprague-Dawley rats (Shell, 1983) did not reflect any maternal or developmental toxicity at the highest dose tested, 30 mg/kg/day.

Mutagenicity

- The mutagenic potential of cyanazine has not been investigated adequately, and only limited information was available for evaluation.

- A study by Dean et al. (1974a) using technical cyanazine (80% a.i.) in mice of both sexes did not reflect any increase in chromosomal aberrations in the bone marrow cells. The animals were examined at

8- and 24-hour intervals after oral dosing with 50 or 100 mg/kg cyanazine. However, the sensitivity of this test was potentially compromised because the positive control data did not reflect a significant number of aberrations: the percent of cells showing chromatid gaps in the positive control (cyclophosphamide) was not statistically significant at the $p < 0.05$ level (U.S. EPA, 1984b).

- Dean et al. (1974b) used technical cyanazine (purity not specified) to induce dominant lethal effects in male CF1 mice. The test was negative at the dose levels tested (80, 160 and 320 mg/kg). However, this study appeared to be invalid because there was no positive control for comparison of data, and a range-finding test was not performed to select the appropriate dosages used in this study (U.S. EPA, 1984b).

- Cyanazine is a member of the triazine family of herbicides. It is known that the triazines follow similar metabolic pathways (i.e., N-dealkylation, S-dealkylation or O-dealkylation and conjugation with glutathion) that result in common or closely related metabolites. Waters, et al. (1980) noted that a triazine herbicide (atrazine) gave a positive mutagenic response in the *Drosophila* sex-linked recessive lethal test (DRL), although this chemical gave a negative response in an *in vitro* test battery with microorganisms. Hence, the potential for cyanazine to give a positive response in a similar test exists (U.S. EPA, 1984b).

Carcinogenicity

- Cyanazine was not determined to have a carcinogenic potential in a 2-year mouse study (Shell, 1981).

- Cyanazine was not oncogenic in 2-year rat studies by Walker et al. (1970b) or by Simpson and Dix (1973); however, these studies were deficient (see description of these studies under the section entitled Long-term Exposure) and are considered to be inadequate by design to determine the oncogenic potential of cyanazine.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level
in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature for determination of the One-day HA for cyanazine. It is, therefore, recommended that the Ten-day HA value for a 10-kg child, calculated below as 0.10 mg/L (100 ug/L), be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The teratology study in rabbits by Shell Toxicology Laboaratory (1982) has been selected as the basis for determination for the Ten-day HA for cyanazine because it provides a short-term NOAEL (1 mg/kg/day for 13 days) for both maternal and fetal toxicity. This study also reflects the lowest NOAEL when compared with the teratology studies in rats described earlier, two in Fischer 344 rats (Lu et al., 1981; Lochry et al., 1985) and one in Sprague-Dawley rats (Shell, 1983).

Using a NOAEL of 1 mg/kg/day, the Ten-day HA for a 10 kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(1 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.10 \text{ mg/L } (100 \text{ ug/L})$$

where:

1 mg/kg/day = NOAEL based on maternal and fetal effects in rabbits exposed to technical cyanazine orally for 13 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption by a child.

Longer-term Health Advisory

No information was suitable for the determination of the Longer-term HA for cyanazine. It is, therefore, recommended that the adjusted Drinking Water Equivalent Level (DWEL) of 0.02 mg/L (20 ug/L) be used for a 10-kg child as a conservative estimate for the Longer-term HA value and the DWEL of 0.07 mg/L (70 ug/L), calculated below, be used for a 70-kg adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Five chronic studies were available for evaluation: (1) a 2-year oncogenic study in mice (Shell, 1981) with a potential NOAEL of 50 ppm (approximately 7.5 mg/kg/day when using a conversion factor for food consumption of 15% of the body weight); (2) a 2-year feeding study in dogs (Walker et al., 1970a) with a NOAEL of 1.25 mg/kg/day; (3) a 2-year feeding/oncogenic study in rats (Walker et al., 1970b, also cited in Walker et al., 1974) with a NOAEL of 12 ppm (approximately 0.6 mg/kg/day when using a conversion factor for food consumption of 5% of the body weight); however, this study was considered unacceptable (U.S. EPA, 1984b) due to several deficiencies in the study report (see Long-term Exposure Section); (4) a second 2-year feeding study in rats (Simpson and Dix, 1973), which was also considered inadequate because the control group reflected an effect, i.e., convulsions, that was suggestive of cross-dosing; and recently, (5) a 1-year feeding study in dogs (Dickie, 1986) with a NOAEL of 25 ppm (approximately 0.7 mg/kg/day based on actual mean food consumption of males and females).

The NOAEL in the mouse study (7.5 mg/kg/day) can be considered for this calculation; however, this NOAEL is higher than the NOAEL in the Walker et al. (1970a) dog study (1.25 mg/kg/day) or in the Walker et al. (1970b) rat study (0.6 mg/kg/day). Since this rat study is considered unacceptable and since the second rat study (Simpson and Dix, 1973) appeared to be flawed by the invalidity of the control group, the 2-year dog study (Walker et al., 1970a) was used previously for the Lifetime HA calculations, using a NOAEL of 1.25 mg/kg/day. This study was of marginal acceptability because only a summary report was available for evaluation and histopathological data were missing for 1/4 females at 1.25 mg/kg/day. However, this NOAEL was supported by a similar NOAEL from a 13-week rat subchronic feeding study by Walker and Stevenson (1968b). Thus using this NOAEL from both studies (i.e., the 2-year dog study and 13-week rat study) and applying a large uncertainty factor of 1,000-fold was appropriate for the calculation of the RfD and the Lifetime HA (in the absence of more adequate chronic studies at that time). At the present time, the new 1-year dog feeding study by Dickie (1986) is a more adequate study for these calculations.

The NOAEL of 25 ppm (equivalent to 0.7 mg/kg/day based on mean actual food consumption in male and female dogs) from the Dickie study (1986) is used in the calculation of the RfD. In this 1-year study, thirty male and female dogs (6 animals/sex/dose) were fed diets containing 0, 10, 25, 100 or 200 ppm cyanazine (98% a.i.). These doses were equivalent to actual mean intakes of 0, 0.27, 0.68, 3.20 or 6.11 mg/kg/day in males and 0, 0.28, 0.72, 3.02 or 6.39 mg/kg/day in females, respectively. No systemic toxicity was noted at 25 ppm (0.7 mg/kg/day) in both sexes. The LOAEL was 100 ppm (3.1 mg/kg/day) based on reduced body weights and body weight gains, elevated platelet counts, and reduced levels of total protein, albumin and calcium in males and females. There were also slight, not statistically significant, decreases in spleen weights and increases in liver weights in the females and increases in liver weights and decreases in testes weights in the males. No gross or microscopic findings related to treatment were noted.

Using a NOAEL of 0.7 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.7\ \text{mg/kg/day})}{(300)} = 0.002\ \text{mg/kg/day}$$

where:

0.7 mg/kg/day = NOAEL based on absence of toxicity in the dog during the one-year feeding exposure.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = modifying factor used to compensate for the lack of a chronic rat study as required by the Office of Pesticide Programs.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.002\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.07\ \text{mg/L}\ (70\ \text{ug/L})$$

where:

0.002 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption by an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.07 mg/L) (20%) = 0.014 mg/L (10 ug/L)

where:

0.07 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Available toxicity data indicate that cyanazine was not carcinogenic in mice (Shell, 1981) or rats (Walker et al., 1970b, 1974; Simpson and Dix, 1973); however, in the rat, some increases were noted in the incidences of both thyroid tumors (male and female rats) and adrenal tumors (male rats); however, these increases were not statistically significant.
- Cyanazine is a chloro-s-triazine derivative that has a chemical structure analagous to atrazine, propazine and simazine. These three analogs were found to significantly ($p < 0.05$) increase the incidence of mammary tumors in rats and they are classified as group C oncogens. Based on structure-activity relationship, cyanazine may reflect a similar pattern of toxicity in the rat. A new 2-year oncogenic study is required from the manufacturer of this chemical to fill this data gap in the toxicity profile of cyanazine.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), cyanazine may be classified in Group D: not classified. This category is used for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- U.S. EPA Office of Pesticide Programs (OPP) has established residue tolerances for cyanazine ranging from 0.05 to 0.10 ppm in or on raw agricultural commodities (U.S. EPA, 1985) based on a Provisional ADI (PADI) of 0.0013 mg/kg/day.

VII. ANALYTICAL METHODS

- Analysis of cyanazine is by a high-performance liquid chromatographic (HPLC) method applicable to the determination of cyanazine in water samples, Method #4 (U.S. EPA, 1986b). In this method, 1 L of sample is extracted with methylene chloride using a separatory funnel. The methylene chloride extract is dried and concentrated to a volume of 10 mL or less. HPLC is used to permit the separation of compounds and measurement is conducted with an ultraviolet (UV) detector. Using this method, the estimated detection limit for cyanazine is 0.3 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) adsorption will remove cyanazine from water.
- Whittaker (1980) experimentally determined adsorption isotherms for cyanazine on GAC.
- GAC adsorption appears to be an effective method of cyanazine removal from water. However, selection of individual or combinations of technologies to attempt cyanazine removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs

August, 1988

DCPA (Dacthal)

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

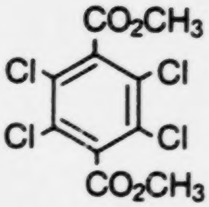
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1861-32-1

Structural Formula



Dimethyl tetrachloroterephthalate

Synonyms

- 2,3,5,6-Tetrachlorodimethyl-1,4-benzenedicarboxylic acid; DCPA; Chlorothal; Dacthalor; DAC; DAC-4; DAC-893; DCP (Meister, 1983).

Uses

- Selective pre-emergence herbicide used to control various annual grasses in turf, ornamentals, strawberries, certain vegetable transplants, seeded vegetables, cotton, soybeans and field beans (Meister, 1983).

Properties (Meister, 1983; Windholz et al., 1983; CHEMLAB, 1985)

Chemical Formula	$C_{10}H_6O_4Cl_4$
Molecular Weight	331.99
Physical State (25°C)	Crystals
Boiling Point	--
Melting Point	156°C
Density (°C)	--
Vapor Pressure (25°C)	2.5×10^{-6} mm Hg at 25°C
Specific Gravity	--
Water Solubility (25°C)	0.5 mg/L at 25°C
Log Octanol/Water Partition Coefficient	6.8×10^3
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Dacthal has been found in 386 of 1,995 surface water samples analyzed and in 12 of 982 ground water samples (STORET, 1988). Samples were collected at 584 surface water locations and 844 ground water locations, and dacthal was found in eight states. The 85th percentile of all nonzero samples was 0.39 ug/L in surface water and 0.05 ug/L in ground water sources. The maximum concentration found was 8.74 ug/L in surface water and 0.05 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- In aqueous solutions, dacthal is not very photolabile with a half-life of greater than one week. Dacthal is also stable versus soil photolysis (Registrant Standard Science chapter for dacthal).

- Soil metabolism of dacthal proceeds with a half-life of greater than 2 to 3 weeks. Degradation rate is affected by temperature. No degradation of dacthal has been observed in sterile soils (half-life of 1,590 days) (Registrant Standard Science chapter for dacthal).

- Degradation products of dacthal include monomethyltetrachloroterephthalate (MTP) and tetrachloroterephthalic acid (TTA) (Registrant Standard Science chapter for dacthal).

- TTA has been shown to be very mobile in soils, whereas dacthal is not (Registrant Standard Science chapter for dacthal).

III. PHARMACOKINETICS

Absorption

- Tusing (1963) reported that 3 humans receiving single oral doses of pure dacthal (25 mg) excreted up to 6% of the doses in the urine as metabolites over a 3-day period. When 3 other humans were administered 50 mg doses of dacthal, approximately 12% was excreted in the urine over a similar time period, indicating that at least 12% of a 50 mg dose was absorbed in humans.

- Skinner and Stallard (1963) reported that following administration of single oral doses of dacthal (100 or 1,000 mg/kg) by capsule to dogs, about 97% of the administered doses were eliminated as the parent compound in the feces by 96 hours. Approximately 3% of dacthal was converted to the monomethylester of tetrachloroterephthalic acid (DAC 1449). Two percent was eliminated in the urine and 1% in the feces. Less than 1% (0.07%) of DAC 1449 was converted to tetrachloroterephthalic acid (DAC 954), which was also excreted in the urine. The results indicated that dacthal was absorbed poorly (about 3%) from the gastrointestinal tract of dogs.

Distribution

- Skinner and Stallard (1963) reported that following a single oral dose of dacthal (100 or 1,000 mg/kg) to dogs, there was no storage of dacthal in the kidneys, liver or fat. However, DAC 954 was found in the kidneys. The authors also reported that no dacthal was found in the kidneys or liver of dogs that had been administered dacthal-T (dacthal containing 1.1% of the monomethyl ester and 1.7% of the tetrachlorophthalate) at 10,000 ppm (250 mg/kg/day) in the diet for two years. The kidneys, liver and fat contained DAC 1449, while the kidneys contained DAC 954 only. Both dacthal and DAC 1449 were found in the fat of dogs treated with 10,000 ppm.

Metabolism

- Tusing (1963) reported that humans who took single oral doses of pure dacthal (25 or 50 mg) converted 3 to 4% of the dose to DAC 1449 within 24 hours. After 3 days, approximately 6% of the 25 mg dose and 11% of the 50 mg dose were converted to DAC 1449. At either dose, less than 1% was converted to DAC 954 in the 1- or 3-day time period.

- Skinner and Stallard (1963) reported that in dogs administered single oral doses of dacthal, small amounts were converted to DAC 1449 (3%) or DAC 954 (0.07%).

- Hazleton and Dieterich (1963) reported similar results when dogs were administered dacthal (10,000 ppm; 250 mg/kg bw) in the diet for 2 years.

Excretion

- In human studies (Tusing, 1963), 6% of a single 25 mg oral dose was excreted in urine as DAC 1449 and 0.5% as DAC 954 over a three-day period. Approximately 11% of the 50 mg dose was converted to DAC 1449 and 0.6% was converted to DAC 954. The parent compound was not found in the urine at either dose.

- Skinner and Stallard (1963) reported that following the administration of a single oral dose (100 or 1,000 mg/kg) to dogs, 90 and 97% was eliminated unchanged in the feces at 24 hours and 96 hours, respectively. Approximately 3% was converted to DAC 1449; of this 3%, 2% was eliminated in the urine and 1% in the feces.

IV. HEALTH EFFECTS

Humans

- Tusing (1963) reported that pure dacthal, administered as single 25 mg or 50 mg oral doses to volunteer subjects (3 at each dose), did not cause any observable effects. Assuming 70 kg body weight, these amounts correspond to doses of 0.36 or 0.71 mg/kg. Hemograms, liver, kidney and urine analyses from the six human volunteers were normal.

Animals

Short-term Exposure

- The acute oral LD_{50} for male and female albino rats (Spartan strain) was reported to be greater than 12,500 mg/kg (Wazeter et al., 1974a).

- The acute oral LD_{50} for male and female beagle dogs was reported to be greater than 10,000 mg/kg (Wazeter et al., 1974b).

- Keller and Kundzin (1960) administered pure dacthal to weanling male Sprague-Dawley rats (10/dose) in the diet for 28 days at levels of 0, 0.0082, 0.0824 or 0.824%. Based upon body weight and compound consumption data provided by the investigators, these dietary levels correspond to approximately 0, 7.6, 78.6 or 758 mg/kg/day. Following treatment, no effects on growth, food consumption, survival, body weights, organ weights, gross pathology and histopathology were observed. This study identifies a NOAEL of 758 mg/kg/day (the highest dose tested).

- Keller (1961) reported that oral administration (by capsule) of 800 mg/kg/day of DCPA (88.5% active ingredient) to beagle dogs (two/sex) for 28 days resulted in loss of body weight, reduced appetite, increased liver weight and liver to body weight ratio, centrilobular liver congestion and degeneration.

Dermal/Ocular Effects

- The acute dermal LD_{50} value for albino rabbits was reported to be greater than 10,000 mg/kg (Elsea, 1958). He also reported that dacthal, when applied to rabbit skin, did not cause irritation or sensitization.

- Johnson et al. (1981) applied dacthal (2,000 mg/kg) for 24 hrs to shaved intact or abraded back or flank skin of New Zealand White rabbits (five/sex) in a paste form. Desquamation (which ranged from very slight to slight) and very slight erythema were observed. There was no pathology noted, and dacthal caused only slight irritation in some animals.

- A single application of 3.0 mg of dacthal to the eyes of albino rabbits produced a mild degree of irritation that subsided completely within 24 hours following treatment (Elsea, 1958).

Long-term Exposure

- Goldenthal et al. (1977) fed CD rats (15/sex/dose) disodium dacthal in the diet for 90 days at dose levels of 0, 50, 500, 1,000 or 10,000 ppm. Based upon compound consumption and body weight data provided by the authors, these dietary levels are approximately 0, 3.6, 36.4, 74 or 732 mg/kg/day for males and 0, 4.2, 43.2, 82.3 or 856 mg/kg/day for females. General behavior, appearance, body weight, food consumption, ophthalmoscopic evaluation, hematology, clinical chemistry, urinalysis, gross pathology and histopathology were comparable for treated and control groups. A NOAEL of 10,000 ppm (732 mg/kg/day for males and 856 mg/kg/day for females, the highest dose tested) was identified for this study.

- Hazleton and Dieterich (1963) fed beagle dogs (four/sex/dose) dacthal in the diet at 0, 100, 1,000 or 10,000 ppm for two years. Based upon body weight and food consumption data provided in the report, these dietary levels are approximately 0, 2.6, 17.7 or 199 mg/kg/day for males and 0, 3, 20.7 or 238 mg/kg/day for females. Physical appearance, behavior, food consumption, hematology, biochemistry, urinalysis, organ weight, organ-to-body weight ratio, gross pathology and histopathology were comparable in treated and control groups at all dose levels. A NOAEL of 10,000 ppm (199 mg/kg/day for males and 238 mg/kg/day for females; the highest dose tested) was identified for this study.

- Paynter and Kundzin (1963b) fed albino rats (35/sex/dose; 70/sex for controls) dacthal in the diet for 2 years at 0, 100, 1,000 or 10,000 ppm. Based on food consumption and body weight data provided in the report, these dietary levels correspond approximately to 0, 5, 50 or 500 mg/kg/day. Physical appearance, behavior, hematology, biochemistry, organ weights, body weights, gross pathology and histopathology of treated and control animals were monitored. After 3 months at 10,000 ppm, slight hyperplasia of the thyroid was reported in both sexes. After 1 year, increased hemosiderosis of the spleen of females occurred at 10,000 ppm and there were slight alterations in the centrilobular cells of the liver of both sexes. Kidney weights were increased significantly in males fed 10,000 ppm at the end of the 2-year study. Based on these data, a NOAEL of 1,000 ppm (50 mg/kg/day) was identified.

Reproductive Effects

- Paynter and Kundzin (1964) conducted a two-generation study using albino rats. Animals (8 males/16 females) were fed dacthal in the diet at dose levels of 0, 0.1 or 1.0% for 24 weeks, prior to mating. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 50 or 500 mg/kg/day. This study reported an evaluation of data collected on the second parental generation (P_2) and through weaning of the first litter (F_{2a}). The authors reported that a second litter (F_{2b}) was not obtained. Following treatment, the following indices were evaluated; fertility, gestation, live births and lactation. Since the fertility index was 37% (6/16) at the 1% dose, 75% (12/16) at the 0.1% dose, and only 19% (3/16) in controls, no conclusions could be reached. The lactation index for the 0.1% group was significantly lower than controls. No other adverse reproductive effects were observed.

- Paynter and Kundzin (1963a) performed a one-generation reproduction study in albino rats. Animals were given dacthal in the diet at 0, 1,000 or 10,000 ppm in the diet. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 50 or 500 mg/kg/day. No effects were detected on fertility, gestation, number of live births or lactation. Based on this information a NOAEL of 10,000 ppm (500 mg/kg/day; the highest dose tested) was identified.

Developmental Effects

- Powers (1964) fed pregnant New Zealand White rabbits (six/dose) dietary levels of dacthal-T (0, 1,000 or 10,000 ppm) on days 8 to 16 of gestation. Assuming that 1 ppm in the diet of rabbits is equivalent to 0.03 mg/kg/day (Lehman, 1959), this corresponds to about 0, 30 or 300 mg/kg/day. Following treatment, fetal toxicity (number of live/dead or resorptions), maternal effects (appearance, behavior, body weight) and visceral and skeletal anomalies were evaluated. No adverse effects were observed at any dose level tested. This study identified a developmental NOAEL of 300 mg/kg/day (the highest dose tested).

Mutagenicity

- No significant increase in mutation frequency was observed in *Drosophila melanogaster* larvae that had been fed media containing 0.1 to 10 mM dacthal (Paradi and Lovenyak, 1981).

- Dacthal had no mutagenic activity, with or without activation, in *Salmonella* assays (Auletta et al., 1977), in *in vivo* cytogenetic tests (Kouri et al., 1977b), in DNA repair tests (Auletta and Kuzava, 1977) or in dominant lethal tests (Kouri et al., 1977a).

Carcinogenicity

- Paynter and Kundzin (1963b) fed albino rats (35/sex/dose; 70/sex for controls) dacthal-T for 2 years at dose levels of 0, 100, 1,000 or 10,000 ppm. Based upon compound consumption and body weight provided in the report, these dietary levels correspond approximately to 0, 5, 50 or 500 mg/kg/day. Based on gross and histologic examination, neoplasms of various tissues and organs were similar in type, localization, time of occurrence, and incidence in control and treated animals.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for deriving a One-day HA. The study in humans by Tusing (1963) was not selected since only low doses (0.36 or 0.71 mg/kg) were tested, and longer-term studies in animals suggest the no-effect level may be much higher. It is, therefore, recommended that the Ten-day HA value for the 10-kg child (80 mg/L; calculated below) be used at this time as a conservative estimate of the One-day HA.

Ten-day Health Advisory

The 28-day feeding study in rats by Keller and Kundzin (1960) has been selected to serve as the basis for determination of the Ten-day HA. In this study, no adverse effects on growth, organ weight, food consumption, gross pathology or histopathology were detected at 758 mg/kg/day.

The Ten-day HA for the 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(758 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 75 \text{ mg/L } (80{,}000 \text{ ug/L})$$

where:

758 mg/kg/day = NOAEL, based on absence of effects on growth, organ weight, food consumption, gross pathology or histopathology in rats fed dacthal for 28 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

No studies were found in the available literature that were suitable for deriving the Longer-term HA value for dacthal. It is, therefore, recommended that the Drinking Water Equivalent Level (DWEL) of 20 mg/L (20,000 ug/L), calculated below, be used for the Longer-term HA value for an adult, and that the DWEL adjusted for a 10-kg child, 5.0 mg/L (5,000 ug/L), be used for the Longer-term HA value for a child.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year study in rats by Paynter and Kundzin (1963b) has been selected to serve as the basis for determination of the Lifetime HA value for dacthal. This study identified a NOAEL of 50 mg/kg/day, based on absence of effects on appearance, behavior, hematology, blood chemistry, organ weight, body weight, gross pathology and histopathology in male rats. The LOAEL was 500 mg/kg/day, based on thyroid hyperplasia, histological changes in the liver and increased kidney weights.

Using this study, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(50\ \text{mg/kg/day})}{(100)} = 0.5\ \text{mg/kg/day}$$

where:

50 mg/kg/day = NOAEL, based on absence of toxic effects in rats exposed to dacthal in the diet for two years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.5\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 17.5\ \text{mg/L}\ (2000\ \text{ug/L})$$

where:

0.5 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (17.5 mg/L) (20%) = 3.5 mg/L (4,000 ug/L)

where:

17.5 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Paynter and Kundzin (1963b) fed dacthal to rats for 2 years and reported no evidence of carcinogenic effects at dose levels up to 10,000 ppm (450 mg/kg/day for males and 555 mg/kg/day in females). This study is limited in that the relatively small numbers of animals used (35/sex/dose; 70/sex for controls) and the removal of animals (10/sex/dose; 20/sex for controls) for interim sacrifice may have resulted in there being too few animals available for observation of late-developing tumors.
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of dacthal.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), dacthal may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA has established residue tolerances for dacthal in or on raw agricultural commodities that range from 0.5 ppm to 15.0 ppm (U.S. EPA, 1985).

VII. ANALYTICAL METHODS

- Analysis of dacthal is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated pesticide in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using an electron capture detector. This method has been validated in a single laboratory and estimated detection limits have been determined for the analytes in the method, including dacthal. The estimated detection limit is 0.02 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Reverse osmosis (RO) is a promising treatment method for pesticide-contaminated waters. As a general rule, organic compounds with molecular weights greater than 100 are candidates for removal by RO. Larson et al. (1982) report 99% removal efficiency of chlorinated pesticides by a thin-film composite polyamide membrane operating at a maximum pressure of 1,000 psi and a maximum temperature of 113°F. More operational data are required, however, to specifically determine the effectiveness and feasibility of applying RO for the removal of dacthal from water. Also, membrane adsorption must be considered when evaluating RO performance in the treatment of dacthal-contaminated drinking water supplies.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

DALAPON

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 75-99-0

Structural Formula

$$CH_3CCl_2COOH$$

(2,2-Dichloropropionic acid)

Synonyms

- Dalapon (ANSI, BSI, WSSA), DPA, Basfapon and Basfapon B (discontinued by BASF Wyandotte); Basfapon/Basfapon N, BH Dalapon and Crisapon (Crystal Chemical Inter-America); Dalapon 85, Dalapon-Na, Ded-Weed and Devipon (Devidayal); Dowpon, Dowpon M, Gramevin and Radapon (discontinued by Dow); Revenge (Hopkins); Unipon (Meister, 1984).

Uses

- Dalapon (2,2-dichloropropionic acid) is used as a herbicide in the form of its sodium and/or magnesium salts to control grasses in crops, drainage ditches, along railroads and in industrial areas (U.S. EPA, 1984).

Properties (U.S. EPA, 1984; Reinert and Rogers, 1987)

Chemical Formula	$C_3H_4Cl_2O_2$
Molecular Weight	143 (acid form)
Physical State (room temp.)	liquid
Boiling Point	185 to 190°C
Melting Point	20°C
Density (°C)	--
Vapor Pressure	--
Specific Gravity	--
Water Solubility (25°C)	50,000 mg/L
Log Octanol/Water Partition Coefficient	1.47
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Dalapon has been found in none of the surface water or ground water samples analyzed from 14 samples taken at 14 locations (STORET, 1988).

Environmental Fate

- The sodium salt of dalapon has been shown to hydrolize slowly in water to produce pyruvic acid, and the rate of hydrolysis increases with increasing temperature. After 175 hours, the extent of hydrolysis at 25°C for 1%, 5% and 18% dalapon solutions was 0.41%, 0.61% and 0.8%, respectively (Brust, 1953).

- Hydrolysis of solutions of either dalapon or dalapon sodium salt is accelerated at alkaline pH values. For example, hydrolysis of dalapon sodium salt at 60°C was 20% complete in 30 hours at which time the equilibrium pH was 2.3. In contrast, hydrolysis was 50% complete in 30 hours when the pH was maintained at 12 during the experiment (Tracey and Bellinger, 1958).

- Based on reaction rate studies, Kenaga (1974) concluded that both dalapon salt and dalapon would have chemical hydrolysis half-lives of several months at temperatures less than 25°C and at initial solution concentrations of less than 1%. Considering the more rapid rate of microbial degradation, those authors concluded that it does not appear that chemical hydrolysis of dalapon is a particularly significant degradative pathway in soils.

- Because of its high water solubility and lack of affinity for soil particles, appreciable adsorption of dalapon on suspended or bottom sediments is not expected in natural waters. Chemical degradation and volatilization probably occur too slowly to account for substantial loss of dalapon from water. Aquarium studies conducted by Smith et al. (1972) provide evidence that volatility is not a route for significant loss of dalapon from water.

- Microbial degradation is by far the most important process affecting the fate of dalapon in soil. Other processes which are of lesser importance are adsorption, leaching and runoff, chemical degradation and volatilization. Based on the light absorption characteristics of aqueous solutions of sodium salts of dalapon, it has been concluded that photodecomposition of dalapon in field applications is improbable (Kearney et al., 1965).

- Although dalapon is subject to hydrolysis under field conditions, chemical degradation is considered to be very slow and is unlikely to be an important factor in the dissipation of dalapon from soil. Smith et al. (1957) and Brust (1953) demonstrated that dalapon and its sodium salt can undergo hydrolysis to pyruvate and HCl.

- Although the laboratory studies indicate that dalapon is a highly mobile compound (Warren, 1954; Helling, 1971; Kenaga, 1974) and should be readily leachable from soils, field data show that under many practical conditions dalapon does not move beyond the first six-inch depth of soil. This is probably because microbial action proceeds at a faster rate than leaching under favorable conditions (Kenaga, 1974).

- The microbial degradation of dalapon in soil has been well established. Thiegs (1955) compared the rates of degradation of dalapon in autoclaved and non-autoclaved soils. The concentration of dalapon (59 ppm) in the autoclaved soil did not change after incubation at 100°F for 1 week while in the unsterilized soil, dalapon disappeared in 4 to 5 weeks after one application and in 1 week after the second application of 50 ppm. Based on the observations that dalapon decomposition is adversely affected by low soil moisture, low pH, temperatures below 20° to 25°C, and large additions of organic matter, Holstun and Loomis (1956) concluded that dalapon degradation was a function of microbiological activity.

III. PHARMACOKINETICS

Absorption

- In both dogs and humans, orally administered dalapon is quickly excreted in the urine. Dogs administered a single oral dose of 500 mg/kg dalapon sodium salt excreted 65 to 70% of the administered dose in 48 hours (Hoerger, 1969). In a 60-day feeding study, dogs receiving 50 and 100 mg/kg of dalapon sodium salt excreted 25 to 53% of the administered dose in the urine (Hoerger, 1969). Human subjects consuming five successive daily oral doses of 0.5 mg of dalapon sodium salt excreted approximately 50% of the administered dose over an 18-day period (Hoerger, 1969). These data suggest that dalapon is well absorbed from the gastrointestinal tract.

Distribution

- Chronic oral administration of dalapon did not result in significant bioaccumulation in either rats or dogs (Paynter et al., 1960). In both rats and dogs, the highest levels of dalapon were found in the kidneys, followed by the muscle and the fat (Paynter et al., 1960).

Metabolism

- Although inadequate data are available to characterize dalapon metabolism in humans, data in cattle (Redemann and Hanaker, 1959) suggest that dechlorination may be involved in the metabolism of dalapon.

Excretion

- Available information suggests that at least 50% of orally administered dalapon is eliminated via the kidneys in dogs and humans (Hoerger, 1969).

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- No information on the short-term health effects of dalapon in humans was found in the available literature.

Long-term Exposure

- No information on the long-term health effects of dalapon in humans was found in the available literature.

Animals

Short-term Exposure

- The sodium salt of dalapon is relatively nontoxic, with an oral LD_{50} ranging from 3,860 mg/kg in the female rabbit to 7,570 mg/kg in the female rat (Paynter et al., 1960).

Dermal/Ocular Effects

- Concentrated sodium dalapon solutions have been found to be irritating to the skin and eyes of rabbits (Paynter et al., 1960).

Long-term Exposure

- In a 90-day dietary study by Paynter et al. (1960), male and female rats were exposed to sodium dalapon (65% pure) at levels of 0, 11.5, 34.6, 115, 346 or 1,150 mg/kg/day. Increases in kidney and liver weight were observed in both sexes at 346 and 1,150 mg/kg/day. The No-Observed-Adverse-Effect Level (NOAEL) in this study was identified as 11.5 mg/kg/day based on increases in kidney weight at higher doses. (See discussion under Longer-term Health Advisory below.)

- In a 1-year study, sodium dalapon (65% pure) was administered to dogs by capsule at levels of 0, 15, 50 or 100 mg/kg/day. Based on increases in kidney weight at 100 mg/kg/day, the NOAEL was identified as 50 mg/kg/day (Paynter et al., 1960).

- With the exception of an increase in kidney weight in male rats, sodium dalapon (65% pure) was without effect in a 2-year dietary study (Paynter et al., 1960); the NOAEL in this study was 15 mg/kg/day. (See discussion under Longer-term Health Advisory below.)

Reproductive Effects

- Administered in the diet, sodium dalapon (65% pure) had no effects on reproduction in the rat at dose levels of approximately 30, 100 or 300 mg/kg/day (Paynter et al., 1960).

Developmental Effects

- Sodium dalapon (purity not specified) was not teratogenic in the rat at doses as high as 2,000 mg/kg/day (Emerson et al., 1971; Thompson et al., 1971). (See Ten-day Health Advisory below.)

Mutagenicity

- Dalapon was not mutagenic in a variety of organisms including Salmonella typhimurium, Escherichia coli, T4 bacteriophage, Streptomyces coelicolor and Aspergillus nidulans (U.S. EPA, 1984). Although Kurinnyi et al. (1982) reported that dalapon increased chromosome aberrations in mice, the inadequate technical detail presented precluded an evaluation of this study.

Carcinogenicity

- No evidence of a carcinogenic response was observed in a 2-year chronic feeding study in which sodium dalapon (65% pure) was administered to rats at levels as high as 50 mg/kg/day for a period of 2 years (Paynter et al., 1960).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were found in the available literature that were suitable for determination of the One-day HA value for dalapon. It is, therefore, recommended that the Ten-day HA value for a 10-kg child (4 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The rat teratology study by Emerson et al. (1971) has been selected to serve as the basis for determination of the Ten-day HA for a 10-kg child. In this study, sodium dalapon (purity not specified; assumed to be 100%) was orally administered to pregnant rats over a 10-day period (days 6 through 15 of gestation) at doses of 0, 500, 1,000 or 1,500 mg/kg/day. Although no compound-related teratogenic response was seen, there was a decreased in weight gain in the dams at the lowest level tested, 500 mg/kg/day. Decreased weight gain was also observed in the pups, but only at higher levels (1,000 and 1,500 mg/kg/day). Standards for dalapon are commonly expressed in terms of the acid rather than the salt. Thus, it is necessary to convert the LOAEL for the sodium salt, 500 mg/kg/day, to the equivalent value for the acid.

$$\text{The LOAEL for dalapon as acid} = \frac{(500\ \text{mg/kg/day})\ (143)}{165} = 430\ \text{mg/kg/day}$$

where:

500 mg/kg/day = LOAEL for sodium dalapon.

143 = molecular weight of dalapon as acid in g/MWt.

165 = molecular weight sodium dalapon in g/MWt.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(430\ \text{mg/kg/day})\ (10\ \text{kg})}{(1{,}000)\ (1\ \text{L/day})} = 4.3\ \text{mg/l}\ (4{,}000\ \text{ug/L})$$

where:

430 mg/kg/day = LOAEL for dalapon as acid based on body weight decreases in dams.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The results of Paynter et al. (1960) suggest that the subchronic and chronic toxicity of dalapon are much the same. Specifically, in a 97-day rat subchronic dietary study, sodium dalapon (65% sodium dalapon; 16% sodium salts of related chloropropionic acids; 2% sodium pyruvate; 5% sodium chloride; 5% water; 7% undetermined) produced an increase in kidney weight in female rats at 34.6 mg/kg/day and higher exposure levels but not at 11.5 mg/kg/day (NOAEL). Similarly, in a two-year rat chronic dietary study, sodium dalapon exposure (65% pure) resulted in an increase in male kidney weight at 50 mg/kg/day but not at 15 mg/kg/day (NOAEL). Considering both Paynter et al. (1960) rat dietary studies together, the 15 mg/kg/day NOAEL for sodium dalapon is appropriate to calculate both a Longer-term HA and a Lifetime HA.

It is customary to express dalapon standards in terms of the acid rather than the salt. The NOAEL used to derive the Longer-term HA is based on studies (Paynter et al., 1960) in which rats were exposed to sodium dalapon that was 65% pure. Thus, a NOAEL for dalapon as the pure acid must be calculated:

$$\text{The NOAEL for dalapon as pure acid} = \frac{(15 \text{ mg/kg/day})\ (0.65)\ (143)}{165} = 8 \text{ mg/kg/day}$$

where:

15 mg/kg/day = NOAEL for 65% pure sodium dalapon.

0.65 = purity of sodium dalapon used in determining NOAEL.

143 = molecular weight of dalapon as acid.

165 = molecular weight of sodium dalapon.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(8 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (3)\ (1 \text{ L/day})} = 0.26 \text{ mg/L } (300 \text{ ug/L})$$

where:

8 mg/kg/day = NOAEL based on kidney weight increases in male rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from animal study.

3 = additional uncertainty factor of 3 to allow for deficiencies in the quality of the data base.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(8 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (3)\ (2 \text{ L/day})} = 0.9 \text{ mg/L } (900 \text{ ug/L})$$

where all factors are the same except:

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

As discussed under Longer-term HA above, the data used to determine the Lifetime HA are identical to those used to determine the Longer-term HA. Using the NOAEL of 8 mg/kg/day from the 2-year rat study by Paynter et al. (1960), the Lifetime HA for the 70-kg adult is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(8 \text{ mg/kg/day})}{(100)\ (3)} = 0.03 \text{ mg/kg/day}$$

where:

8 mg/kg/day = NOAEL for 100% dalapon as acid.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = additional uncertainty factor of 3 to allow for deficiencies in the quality of the data base.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.03 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.9 \text{ mg/L } (900 \text{ ug/L})$$

where:

0.03 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.9 mg/L) (20%) = 0.18 mg/L (200 ug/L)

where:

0.9 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenicity was found in a 2-year dietary study in which sodium dalapon was administered to rats at levels as high as 50 mg/kg/day (Paynter et al., 1960).

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), dalapon may be classified in Group D: not classified. This group is for substances with inadequate human and animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The American Conference of Governmental Industrial Hygienists suggests a Threshold Limit Value (TLV) of 1 ppm (6 mg/m^3) as a time-weighted average for an 8-hour work day.

- Tolerances have been established for dalapon in a wide variety of agricultural commodities (CFR, 1985) ranging from 0.1 ppm in milk to 75 ppm in flaxseed.

VII. ANALYTICAL METHODS

- Analysis of dalapon is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated acid pesticides in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is acidified. The compounds are extracted with ethyl ether using a separatory funnel. The derivatives are hydrolyzed with potassium hydroxide, and extraneous organic material is removed by a solvent wash. After acidification, the acids are extracted and converted to their methyl esters using diazomethane as the derivatizing agent. Excess reagent is removed, and the esters are determined by electron-capture GC. The method detection limit has not been determined for this compound.

VIII. TREATMENT TECHNOLOGIES

- No information on treatment technologies capable of effectively removing dalapon from contaminated water was found in the available literature.

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DIAZINON

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

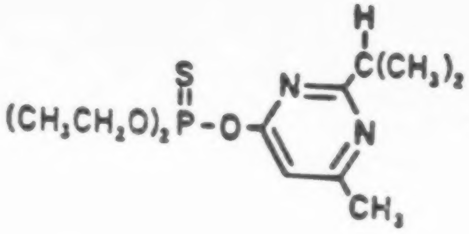
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 333-41-5

Structural Formula



0,0-Diethyl-0-(2-isopropyl-4-methyl-6-pyrimidinyl)phosphorothiote

Synonyms

- Antigal; AG-500; Basudin; Bazudin; Ciazinon; Ducutox; Dassitox; Dazzel; Dianon; Diater; Diaterr-Fos; Diazajet; Diazide; Diazitol; Diazol; Dicid; Dimpylat; Dizinon; Dyzol; Exodin; Flytrol; Galesan; Kayazinon; Necidol/Nucidol; R-Fos; Spectacide; Spectracide (Meister, 1985).

Uses

- Soil insecticide; insect control in fruit, vegetables, tobacco, forage, field crops, range, pasture, grasslands and ornamentals; nematocide in turf; seed treatment and fly control (Meister, 1985).

Properties (Meister, 1983; Windholz et al., 1983)

Chemical Formula	$C_{12}H_{21}O_3N_2SP$
Molecular Weight	304.36
Physical State (25°C)	Colorless oil
Boiling Point	83 to 84°C (0.002 mm Hg)
Melting Point	--
Density	--
Vapor Pressure (20°C)	1.4×10^{-4}
Water Solubility (20°C)	40 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Diazinon has been found in 6,026 of 22,291 surface water samples analyzed and in 74 of 3,633 ground water samples (STORET, 1987). Samples were collected at 3,555 surface water locations and 2,835 ground water locations, and diazinon was found in 46 states. The 85th percentile of all nonzero samples was 0.01 ug/L in surface water and 0.25 ug/L in ground water sources. The maximum concentration found was 33,400 ug/L in surface water and 84 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- ^{14}C-Diazinon (99% pure), at 7 or 51 ppm on sandy loam soil, degraded with a half-life of 37.4 hours after exposure to natural light (Blair, 1985). The degradate, oxypyrimidine, was detected at a maximum concentration of 19.60% (13.5 hours) of applied material when exposed to natural sunlight. After 35.5 hours (37.4 hours is the half-life) of sunlight exposure, 20.7% of the radiolabeled material was in soil-bound residues (some of which contained oxypyrimidine), 24.4% was oxypyrimidine and 39.7% diazinon. Losses of 7% were attributed to volatilization of diazinon and degradates (of which 0.5% was carbon dioxide). The total ^{14}C-radioactive material balance was 87-89% at the 0 hour and 84% at all other experimental points.

- ^{14}C-Diazinon (99% pure) degraded in sandy loam soil with a half-life of 17.3 hours when exposed to natural sunlight (Martinson, 1985). The degradate, oxypyrimidine, was detected at maximum concentrations of 23.72% (32.6 hours) of applied after exposure to natural sunlight. The degradate 2-(1'-hydroxy-1'-methyl)ethyl-4-methyl-6-hydroxypyrimidine was present after 8 hours of natural sunlight exposure at 3.6% of the applied material but was not present in the non-exposed samples. An unidentified degradate resulting from non-photolytic degradation (since it was also present in non-exposed samples), accounted for about 7% of the applied material under sunlight.

- In a Swiss sandy loam soil at 75% of field capacity and 25°C, ring-labeled ^{14}C-diazinon (97% pure) applied at 10 ppm rapidly degraded to 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMHP) with a half-life of less than one month. Within 14 days only 12.3% of the activity was found as the parent; 72.9% was identified as IMHP. Breakdown of IMHP was slower than that of diazinon and 49% of the applied radioactive material was in the form of IMHP after 84 days. After 166 days the amount of IMHP decreased to 4.7% of the applied material. Increased recoveries of $^{14}CO_2$ (55.6% after 166 days) and unextracted ^{14}C residues

(15.1% after 166 days) corresponded to IMHP breakdown. No other major metabolites were found. Radioactivity in the H_2SO_4 and ethylene glycol traps was <1% of the applied ^{14}C throughout the study and material balance was generally above 80% of the applied material (Keller, 1981).

III. PHARMACOKINETICS

Absorption

- Mucke et al. (1970) reported that in both male and female rats, 69 to 80% of orally administered diazinon is excreted in the urine within 12 hours. This indicates that diazinon is well absorbed from the gastrointestinal tract.

Distribution

- The retention of diazinon labeled with ^{14}C in the pyrimidine ring and in the ethoxy groups was investigated in Wistar rats (Mucke et al., 1970). Doses of 0.1 mg/rat were administered by stomach tube daily for 10 days. Tissue levels 8 hours after the final dose were as follows: stomach and esophagus, 0.25%; small intestine, 0.65%; cecum/colon, 0.76%; liver, 0.16%; spleen, 0.01%; pancreas, 0.01%; kidney, 0.04%; lung, 0.02%; testes, 0.02%; muscle, 0.77% and fat, 0.23%.

- Chickens were fed diazinon at levels of 2, 20 or 200 ppm in their food for a period of 7 weeks (Mattson and Solga, 1965). Assuming that 1 ppm in the diet of chickens is equivalent to 0.125 mg/kg/day, this corresponds to doses of about 0.25, 2.5 or 25 mg/kg/day (Lehman, 1959). At the end of the feeding period, tissues from the animals fed 200 ppm (25 mg/kg/day) in the diet were analyzed for diazinon. There was no diazinon detected in fat, white or dark muscle, heart, kidney, liver, gizzard or eggs. The limit of sensitivity of the method was 0.05 ppm. There appeared to be no accumulation of diazinon in the body at 200 ppm (25 mg/kg/day) in the diet.

Metabolism

- The metabolism of diazinon ^{14}C-labeled in the pyrimidine ring was investigated in Wistar rats (200 g) after administration by stomach tube (Mucke et al., 1970). In addition to some unchanged diazinon, three major metabolites, all with the pyrimidine ring intact, were identified in the urine, and to a lesser degree in the feces. A fourth fraction containing polar materials was also found. The three main metabolites were the result of a split at the oxygen-phosphorus bond, with subsequent hydroxylation of the isopropyl side chain. There was no significant expiration of labeled carbon dioxide, further indicating that the pyrimidine nucleus remained intact.

- The metabolism of diazinon was investigated *in vitro* in rat liver microsomes obtained from adult male rats (Nakatsugawa et al., 1969).

It was found that diazinon underwent a dual oxidative metabolism consisting of activation to diazoxon and degradation to diethyl phosphorothioic acid. The authors noted that they had observed similar pathways in studies with parathion and malathion, and these results emphasized the importance of microsomal oxidation in the degradation of organophosphate esters, indicating that many of the so-called phosphatase products or hydrolysis products may actually be oxidative metabolites.

Excretion

- The excretion of diazinon labeled with ^{14}C in the pyrimidine ring and in the ethoxy groups was investigated after administration by stomach tube to Wistar rats (Mucke et al., 1970). The diazinon was excreted rapidly by both male and female animals, and 50% of the administered dose was recovered within 12 hours. Of this, 69 to 80% was excreted in the urine, and 18 to 25% in the feces. There was negligible expiration of labeled carbon dioxide. There was no evidence of accumulation of diazinon in any tissue.

IV. HEALTH EFFECTS

- Diazinon is a reactive organophosphorus compound, and many of its toxic effects are similar to those produced by other substances of this class. Characteristic effects include inhibition of acetyl cholinesterase (ChE) and central nervous system (CNS) depression.

Humans

Short-term Exposure

- Wedin et al. (1984) described a case report of diazinon poisoning in a 26-year-old man who deliberately ingested a preparation containing an unknown concentration of diazinon in an apparent suicide attempt. Upon admission to the hospital, the patient exhibited most of the usual symptoms of organophosphate poisoning, including muscarinic, nicotinic and CNS manifestations. During treatment and monitoring, it was noted that the urine output was very low and was dark and cloudy in appearance. By the second day, the urine was found to contain moderate amorphous crystals that could not be identified. With increased intravenous fluids, the urine output increased, but the crystaluria persisted and increased up to the 4th day, with a gradual decrease for the next 5 days, at which time the patient was discharged. Serum creatinine and urea nitrogen levels remained normal throughout this period. It was noted that this phenomenon may have been related to the specific pesticide formulation that had been ingested, but the authors suggested that renal function should be monitored more closely in persons with organophosphate poisoning.

- Two men reportedly developed "marked" inhibition of plasma ChE following the administration (route not specified) of five doses of 0.025 mg/kg/day. A dose of 0.05 mg/kg/day for 28 days reduced plasma ChE in three men by 35 to 40%. In other tests, each involving three to four men, doses ranging from 0.02 to 0.03 mg/kg/day produced reductions in plasma cholinesterase activity of 0, 15 to 20 and 14%. In no case was there any effect on red blood cell cholinesterase activity or on hematology, serum chemistry or urinalysis. Thus, 0.02 mg/kg/day was identified as a No-Observed-Adverse Effect Level (NOAEL) in humans (FAO/WHO, 1967, cited in Hayes, 1982).

Long-term Exposure

- No information was found in the available literature on the long-term health effects of diazinon in humans.

Animals

Short-term Exposure

- The acute oral toxicity of diazinon MG8 (a yellow oily liquid, 1,200 mg/mL) was studied in male albino rats (238 to 321 g) by DeProspo (1972). Four groups of six rats each were given a single dose of diazinon by gavage and then observed for 7 days. Dose levels administered were 157, 313, 625 or 1,250 mg/kg. Within 4 hours of administration, animals at the three higher levels displayed symptoms of lethargy, tremors, convulsions and runny noses. Mortality in the four groups was 0/6, 2/6, 5/6 and 6/6, respectively, with death occurring between 8 and 24 hours after exposure. At 2 days, the remaining animals at the two intermediate levels had recovered. There was no mention of adverse symptoms at the lowest dose level. Gross necropsy (performed only on animals that died) did not reveal abnormal findings. The acute oral LD_{50} value was calculated to be 395.6 mg/kg.

- Hazelette (1984) investigated the effects of dietary hypercholesteremia (HCHOL) on sensitivity to diazinon in inbred male C56BL/6J mice. The LD_{50} of diazinon in HCHOL mice was nearly half that of diazinon administered to normal mice (45 versus 84 mg/kg). Cholesterol feeding increased ChE activity in both blood and liver, and these increases were negated by diazinon. Hepatic diazinon levels were also higher in the HCHOL animals. It was concluded that HCHOL resulted in an increase in susceptibility to, and toxicity of, diazinon.

- Adult mongrel dogs (one/sex/dose) were fed diazinon (0 or 1.0 ppm in the diet) for a period of 6 weeks (Doull and Anido, 1957). Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day, this corresponds to doses of about 0 or 0.025 mg/kg/day (Lehman, 1959). Serum and erythrocyte ChE determinations were made on a weekly basis before and during exposure. Neither plasma nor red blood cell ChE varied by more than ±15% from control in exposed animals of either sex, and there were no observed changes in body weight for the test period. The apparent NOAEL for this study, based on blood chemistry parameters, is 0.025 mg/kg.

- The effect of diazinon (tech. grade) on blood cell ChE activity was investigated in sheep after the administration of single oral doses by gavage of 50, 65, 100, 200 or 250 mg/kg (Anderson et al., 1969). Twenty-six sheep were used in the study groups. Prior to dosing, 245 untreated sheep were used to determine the normal range of erythrocyte ChE values. A typical severe clinical response consisted of profuse salivation, ataxia, dyspnea, dullness, anorexia and muscle twitching. In mild cases, only dullness and anorexia were seen, but were sufficiently pronounced to enable differentiation between normal and affected animals. Sheep that were clinically affected by diazinon suffered a depression of ChE of more than 75%. However, there were five animals (at the 50-mg/kg dose level) that tolerated depressions of 80 to 90% without clinical effect. The ChE values fell to minimum values within 1 to 4 hours, and remained close to this level until about 8 hours after dosing, during which time symptoms were observed. In those showing maximum depressions of 80% or more, the ChE activity returned to about half its normal value by the 5th day, and thereafter recovered only very slowly during a period of several weeks.

- Davies and Holub (1980a) compared the subacute toxicity of diazinon (approximately 99%) in male and female Wistar rats. The diazinon was incorporated into a semipurified diet at levels of 2 or 25 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, this corresponds to doses of about 0.1 or 1.2 mg/kg/day (Lehman, 1959). Effects on ChE activity were periodically assessed during a 28- to 30-day feeding period. Levels of 25 ppm (1.2 mg/kg/day) diazinon in the diet for 30 days produced more significant reduction of ChE activity in plasma (22 to 30%) and brain (5 to 9%) among treated females compared to treated males. Erythrocyte ChE activity was significantly more depressed (13 to 17%) in treated females relative to males at days 21 to 28 of the feeding period. At no time was ChE activity in any tissue more reduced among treated males than females. At the 2-ppm (0.1 mg/kg/day) dose level for 7 days, diazinon failed to affect erythrocyte ChE activity in either sex relative to controls. Plasma ChE activities of treated males were not significantly different from control values, but treated females showed significant depression (29%) of plasma ChE activity. This investigation indicated that the female rat is more sensitive to the toxicity of dietary diazinon than the male. Based on the inhibition of ChE in the female animals observed at 2 ppm, the Lowest-Observed-Adverse Effect Level (LOAEL) for this study was identified as 0.1 mg/kg/day.

Dermal/Ocular Effects

- Nitka and Palanker (1980) investigated the primary dermal irritation and primary ocular irritation characteristics of a commercial formulation of diazinon in New Zealand White rabbits. The percentage of diazinon in the formulation was not given. After administration of a single application of 0.5 mL to abraded and intact skin of six rabbits, the formulation was judged not to be a primary dermal irritant. Nine rabbits were used to examine the effect of administration of a single dose of 0.1 mL of the formulation in one eye, and the results indicated that it was not an ocular irritant.

Long-term Exposure

- Female Wistar rats were fed a semipurified diet containing 0 or 0.1 to 15 ppm diazinon 99%) for up to 92 days with no visible toxic effects (Davies and Holub, 1980b). Weight gain and food consumption were comparable to controls. Feeding studies up to 90 days revealed that rats were highly sensitive to diazinon after 31 to 35 days of exposure, as judged by reduction in plasma and erythrocyte cholinesterase (ChE) activities. Plasma ChE was judged most sensitive. A NOAEL of 0.1 ppm, which the authors translated to an equivalent daily intake of 9 ug/kg/day, is based on plasma ChE inhibition noted for up to 35 days of feeding.

- Woodard et al. (1965) exposed monkeys (three/sex/dose) to diazinon orally for 52 weeks. The animals were started at doses of 0.1, 1.0 or 10 mg/kg/day for the first 35 days, but these doses were lowered to 0.05, 0.5 or 5.0 mg/kg/day for the remainder of the study, apparently because of poor food consumption and decreased weight gain. During the 52 weeks, body weight gain was slightly depressed in all treated groups, and soft stools were observed in all animals, with diarrhea in three animals (dose not specified). One female at the 0.5-mg/kg dose level had significant weight loss and signs of dehydration, emaciation, pale skin coloration and an unthrifty hair coat. One female at this level (it is not clear whether it is the same animal just mentioned) exhibited decreased hemoglobin and a rapid sedimentation rate at 39 and 53 weeks. Plasma ChE was inhibited 93% at the high dose and 23% at the mid-dose, but no inhibition was noted at 0.05 mg/kg (the low dose). Red blood cell ChE was inhibited 90%, 0% and 0% at the high, mid and low doses, respectively. Other biochemical parameters were normal. Based on inhibition of ChE, a NOAEL of 0.05 mg/kg/day and a LOAEL of 0.5 mg/kg/day were identified in this study.

- Barnett and Kung (1980) fed Charles River CD-1 mice diazinon (87.6%) in the diet at levels of 0, 4, 20 or 100 ppm for 18 months (males) or 19 months (females). Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day, this corresponds to doses of about 0, 0.6, 3 or 15 mg/kg/day (Lehman, 1959). Groups of 60 animals of each sex were used at each treatment level, and a similar group served as controls. In males, there was a significant reduction in weight gain at the highest dose. Weight reduction was significant in all female groups, although it did not appear to be dose- or treatment related. There were no significant trends in mortality. Animals showed skin irritation, loss of hair, skin lesions and piloerection. Gross and microscopic examinations showed no inflammatory, degenerative, proliferative or neoplastic lesions due to the administration of diazinon. A LOAEL of 4 ppm (0.6 mg/kg/day) was identified for the mouse in this study.

- Horn (1955) fed diazinon (25%) to groups of 20 male and 20 female rats at 0, 10, 100 or 1,000 ppm in the diet for 104 weeks. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, this corresponds to dose levels of about 0, 0.5, 5 or 50 mg/kg/day (Lehman, 1959). The rats were started on the diet as weanlings weighing 62 to 63 g. In preliminary studies, the highest dose caused significant growth retardation. The animals for this group were initially given 100 ppm diazinon, which was increased gradually over a period of 11 weeks to the 1,000-ppm level. Mortality occurred in all groups, including the controls, and pneumonia was common. In all groups, body weight and food consumption were comparable to the controls. Hematocrit values for males at 1,000 ppm were significantly depressed when compared to controls. At 10 ppm, plasma ChE was inhibited by 60 to 67%, red blood cell ChE was inhibited 24 to 42% and brain ChE was inhibited 8 to 10%. At 100 or 1,000 ppm, there was 95 to 100% inhibition of ChE in plasma and blood cells. At 100 ppm, brain ChE was inhibited 19 (males) to 53% (females), and this increased to 41 (males) to 59% (females) at 1,000 ppm. There were no significant gross pathological findings. Based on inhibition of blood and plasma ChE, the LOAEL for this study was identified as 10 ppm (0.5 mg/kg/day).

Reproductive Effects

- Johnson and Cronin (1965) conducted a three-generation reproduction study in Charles River rats. Beginning 70 days before mating, groups of 20 females were fed diazinon (as 50% wettable powder) in the diet at 4 or 8 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, this corresponds to doses of about 0.2 or 0.4 mg/kg/day (Lehman, 1959). The end points monitored included: general maternal condition, number of live and dead fetuses, number of pups per litter, mean pup and litter weights, gross pathology of F_{1a}, F_{2a} and F_{3a} animals, and histopathology of F_{3b} animals. All findings were reported to be normal, but there were no detailed data provided. A NOAEL of 8 ppm (0.4 mg/kg/day), the highest dose tested, was identified in this study.

- Diazinon was administered by gavage at dose levels of 0, 7, 25 or 100 mg/kg to groups of 18 to 22 New Zealand White rabbits on days 6 to 18 of gestation (Harris et al., 1981). At the 100-mg/kg level, 9/22 animals died. This was not statistically significant ($p < 0.07$) using the Fisher Exact Test, although it was thought to be biologically significant by the authors. Of these nine animals, seven showed lesions indicative of gastrointestinal toxicity. At this dose, animals also were observed to have tremors and convulsions and were anorexic and hypoactive. These symptoms were not observed in animals at the 7- and 25-mg/kg levels. One rabbit at the 25-mg/kg level aborted on day 27, and all fetuses were dead. At this dose there were no significant changes in weight gain compared to the control, and no changes in the corpora lutea. There were also no statistically significant changes in implantation sites, proportion of live, dead or resorbed fetuses per litter, fetal weights or sex ratios. Based on these data, the NOAEL for reproductive effects for the rabbit was identified as 7 mg/kg/day.

Developmental Effects

- Diazinon at dose levels of 7, 25 or 100 mg/kg was administered by gavage to New Zealand White rabbits on days 6 to 18 of gestation (Harris et al., 1981). Groups of 18 to 22 rabbits, 4 to 5 months of age and weighing 3.0 to 4.1 kg, were given diazinon in 0.2% sodium carboxymethyl cellulose (CMC) and a group of controls was given 0.2% CMC only. At the 100-mg/kg level, 9/22 animals died, and although this mortality was not quite significant ($p < 0.07$) using the Fisher Exact Test, it was thought to be biologically significant by the authors. There were no significant differences in abnormalities between the control and treated groups, and it was concluded that diazinon was neither fetotoxic nor teratogenic in the rabbit at these dose levels. With respect to fetal effects, a NOAEL of 100 mg/kg/day, the highest dose tested was identified. Based on maternal toxicity, a NOAEL of 25 mg/kg/day is identified.

- Tauchi et al. (1979) administered diazinon by gavage to groups of 30 pregnant rats for 11 days (days 7 to 17 of gestation), at dose levels of 0, 0.53, 1.45 or 4.0 mg/kg/day. In each group, 20 animals were delivered by Cesarean section on day 17, while the remaining 10 were allowed to deliver normally. There were no effects on behavior or learning ability, and no pathological lesions were detected at 10 weeks. It was concluded that diazinon was not teratogenic at the doses tested. The NOAEL for fetal effects in this study was 4.0 mg/kg/day, the highest dose tested.

Mutagenicity

- Four strains of Salmonella typhimurium were used to assay the mutagenic potential of diazinon (Marshall et al., 1976). Negative results were found by these investigators as well.

- The mutagenicity of diazinon was tested in bacterial reversion-assay systems with five strains of Salmonella typhimurium and one strain of Escherichia coli (Moriya et al., 1983). No evidence of mutagenic activity was noted in any of the test systems.

- Fritz (1975) conducted a dominant lethal study in NMRI-derived albino mice. Single doses of diazinon were administered orally to males at levels of 15 or 45 mg/kg. After exposure, the males were mated to untreated females several times over a period of 6 weeks. There were no significant differences in mating ratios, the number of implantations or embryonic deaths (resorptions), and no adverse effects were observed in the progeny at either dose level. It was concluded that diazinon did not produce dominant lethal mutations in this test at the doses used.

Carcinogenicity

- A chronic bioassay for possible carcinogenicity of diazinon was conducted in F-344 rats and $B6C3F_1$ mice (NCI, 1979). Groups of 50 animals were fed diazinon in the diet at the following levels: rats, 400 or 800 ppm; mice, 100 or 200 ppm. Assuming that 1 ppm in the diet of rats and mice is equivalent to 0.05 and 0.15 mg/kg/day, respectively, this corresponds to doses of about 20 or 40 mg/kg/day in rats and about 15 or 30 mg/kg/day in mice (Lehman, 1959). There was some hyperactivity noted in animals of both species, but there was no significant effect on either weight gain or mortality. There was no incidence of tumors that could be clearly related to diazinon, and it was concluded that diazinon was not carcinogenic in either species.

- Charles River CD-1 mice were fed diazinon (87.6%) in the diet at levels of 4, 20 or 100 ppm for 18 months (males) or 19 months (females) (Barnett and Kung, 1980). Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day, this corresponds to doses of about 0.6, 3 or 15 mg/kg/day (Lehman, 1959). Groups of 60 animals of each sex were used at each treatment level, and a similar group served as controls. In males at the highest dose level there was a significant difference in weight gain from the controls. Weight reduction was significant in all female treatment groups, but it did not appear to be dose- or treatment-related. There were no significant trends in mortality. Gross and microscopic examinations showed no inflammatory, degenerative, proliferative or neoplastic lesions due to the administration of diazinon, and the study was judged to be negative with respect to carcinogenicity.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value. It is, therefore, recommended that the Ten-day HA value for a 10-kg child (0.02 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The most sensitive indicator of the effects of diazinon is inhibition of ChE. However, this effect is reversible, and significant inhibition of this enzyme often occurs without production of clinically significant effects. Consequently, selection of a NOAEL or LOAEL value based only on inhibition of ChE, in the absence of any other toxic signs, is a highly conservative approach.

The study in humans described by Hayes (1982) has been selected to serve as the basis for determination of the Ten-day HA value for diazinon. Although this study is a secondary source, it establishes a NOAEL in humans based on the most sensitive end point, i.e., ChE. Hayes reported that in human volunteers, short-term exposure to doses of 0.02 mg/kg/day did not result in decreased ChE levels, while doses of 0.025 to 0.05 mg/kg/day caused ChE reductions of 15 to 40%. This NOAEL (0.02 mg/kg/day) is supported by studies in animals; e.g., based on blood and serum ChE, Doull and Anido (1957) reported a NOAEL of 0.05 mg/kg/day in a 6-week study in dogs.

Using a NOAEL of 0.02 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.02 \text{ mg/kg/day})\ (10 \text{ kg})}{(10)\ (1 \text{ L/day})} = 0.02 \text{ mg/L } (20 \text{ ug/L})$$

where:

0.02 mg/kg/day = NOAEL, based on absence of ChE inhibition in humans.

10 kg = assumed body weight of a child.

10 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from a human study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The study by Woodard et al. (1965) has been selected to serve as the basis for the Longer-term HA. Based on inhibition of plasma ChE in monkeys exposed for 52 weeks, this study identified a NOAEL of 0.05 and a LOAEL of 0.5 mg/kg/day. These values are supported by the NOAEL for ChE inhibition of 0.025 mg/kg/day identified in a 6-week feeding study in dogs (Doull and Anido, 1957) and by the LOAEL of 0.5 mg/kg/day identified by Horn (1955), based on ChE inhibition in rats exposed for 2 years.

Using a NOAEL of 0.05 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.05 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 0.005 \text{ mg/L } (5.0 \text{ ug/L})$$

where:

0.05 mg/kg/day = NOAEL, based on absence of ChE inhibition in monkeys given diazinon orally for 52 weeks.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Using a NOAEL of 0.05 mg/kg/day, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.05 \text{ mg/kg/day}) (70 \text{ kg})}{(100) (2 \text{ L/day})} = 0.0175 \text{ mg/L } (20 \text{ ug/L})$$

where:

0.05 mg/kg/day = NOAEL, based on absence of ChE inhibition in monkeys given diazinon orally for 52 weeks.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Available lifetime studies were not judged adequate for use in the determination of the Lifetime HAs since toxicological end points and numbers of animals tested were limited. Therefore, the 13-week study of Davies and Holub (1980) has been selected to serve as the basis for determination of the Lifetime HA, with an additional safety factor of 10 for studies of less than a lifetime. This study identified a NOAEL of 0.009 mg/kg/day.

Using a NOAEL of 0.009 mg/kg/day, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.009\ \text{mg/kg/day})}{(100)} = 0.00009\ \text{mg/kg/day}$$

where:

0.009 mg/kg/day = NOAEL, based on plasma cholinesterase inhibition in rats exposed to diazinon in the diet for up to 92 days.

100 = uncertainty factor of 10 for the end point of toxicity-cholinesterase inhibition and an additional factor of 10 for a study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.00009\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.00315\ \text{mg/L}\ (3\ \text{ug/L})$$

where:

0.00009 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.00315\ \text{mg/L})\ (20\%) = 0.00063\ \text{mg/L}\ (0.6\ \text{ug/L})$$

where:

0.00315 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Two studies on the carcinogenicity of diazinon in mice have been reported (NCI, 1979; Barnett and Kung, 1980). Neither study revealed any evidence of carcinogenicity.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of diazinon.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), diazinon may be classified in Group E: evidence of non-carcinogenicity for humans. This category is for substances that show no evidence of carcinogenicity in at least two adequate animal tests or in both epidemiologic and animal studies.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The NAS (1977) has calculated an ADI of 0.002 mg/kg/day, based on a NOAEL in humans of 0.02 mg/kg/day and an uncertainty factor of 10. Assuming average body weight of human adult of 70 kg, daily consumption of 2 liters of water and a 20% contribution from water, NAS (1977) calculated a Suggested-No-Adverse-Effect-Level of 0.014 mg/L.

VII. ANALYTICAL METHODS

- Analysis of diazinon is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using a capillary column GC. Measurement is made using a nitrogen phosphorus detector. This method has been validated in a single laboratory, and estimated detection limits have been determined for the analytes in the method, including diazinon. The estimated detection limit is 0.25 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that reverse osmosis (RO), granular-activated carbon (GAC) adsorption and ozonation will remove diazinon from water. The percent removal efficiency ranged from 75 to 100%.

- Laboratory studies indicate that RO is a promising treatment method for diazinion-contaminated waters. Chian (1975) reported 100% removal efficiency using a cross-linked polyethylenimine (NS-100) membrane and 99.88% removal efficiency with a cellulose acetate (CA) membrane. Both membranes operated separately at 600 psi and a flux rate of 8-12 gal/ft^2/day. Membrane adsorption, however, is a major concern and must be considered as breakthrough of diazinon would probably occur once the adsorption potential of the membrane was exhausted.

- GAC is effective for diazinon removal. Dennis and Kobylinski (1983) and Dennis et al. (1983) reported 94.5%, 90.5% and 76% diazinon removal efficiency from wastewater in 6 hr. treatment periods with 45 lbs of GAC. Also, 95% diazinon removal efficiency was achieved in an 8-hr. treatment period with 40 lbs of GAC.

- Whittaker (1980) experimentally determined GAC adsorption isotherms for diazinon and diazinon-methyl parathion solutions in distilled water indicate that treatment with GAC can be used to remove diazinon.

- UV/O3 oxidation treatment appears to be an effective diazinon removal method. UV/O3 oxidized 75% of diazinon at 3.4 gm/L ozone dosage and a retention time of 204 minutes. When lime pretreatment was used, UV/O3 oxidized 99+% of diazinon at 4.1 gm/L ozone dosage and 240 minutes retention time (Zeff et al., 1984).

- Some treatment technologies for the removal of diazinon from water are available and have been reported to be effective. However, selection of individual or combinations of technologies to attempt diazinon removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

DICAMBA

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

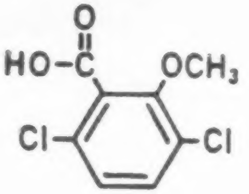
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1918-00-9

Structural Formula



2-Methoxy-3,6-dichlorobenzoic Acid

Synonyms

- Banes, Banex, Banlen, Banvel D, Banvel, Brush buster, Dianat, Dianate, Dicambe, Mediben, Mondak, MDBA, Velsicol Compound R

Uses

- Herbicide used to control broadleaf weeds in field and silage corn, grain sorghum, small grains, asparagus, grass seed crops, turf, pasture, rangeland, and non-cropland areas such as fence rows, roadways and wastelands. For control of brush and vines in non-cropland, pasture and rangeland areas (Berg, 1986).

Properties (Berg, 1986; CHEMLAB, 1985; Windholz et al., 1983; Worthing, 1983; WSSA, 1983)

Chemical Formula	$C_8H_6Cl_2O_3$
Molecular Weight	221.04
Physical State (at 25°C)	Crystals
Boiling Point	--
Melting Point	114 to 116°C
Density	--
Vapor Pressure (20°C)	3.41×10^{-5} mm Hg
Specific Gravity	--
Water Solubility (20°C)	4,500 mg/L at 25°C
Log Octanol/Water Partition Coefficient	3.67 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Dicamba has been found in 262 of 806 surface water samples analyzed and in 2 of 230 ground water samples (STORET, 1988). Samples were collected at 151 surface water locations and 192 ground water locations; dicamba was found in 9 states. The 85th percentile of all non-zero samples was 0.15 ug/L in surface water and 0.07 ug/L in ground water. The maximum concentration found in surface water was 3.3 ug/L, while in ground water it was 0.07 ug/L. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- In several aerobic soil metabolism studies, dicamba (acid or salt form not specified) had half-lives of 1 to 6 weeks in sandy loam, heavy clay, silty clay, clay loam, sand and silt loam soils at 18 to 38°C and 40 to 100% of field capacity. Degradation rates decreased with decreasing temperature and soil moisture (Smith, 1973a,b; Smith, 1974; Smith and Cullimore, 1975; Suzuki, 1978;1979).

- For the dimethylamine salt, half-lives in sandy loam and loam soils ranged from 17 to 32 days (Altom and Stritzke, 1973). Phytotoxic residues, detected by a non-specific bioassay method, have persisted in aerobic soil for almost 2 years (Sheets, 1964; Sheets et al., 1968).

- Based on soil thin-layer chromatography (TLC), dicamba (acid or salt form not specified) is highly mobile in sandy loam, silt loam, sandy clay loam, clay loam, loam, silty clay loam and silty clay soils (Helling, 1971; Helling and Turner, 1968).

- The free acid of dicamba and the dimethylamine salt were not appreciably adsorbed to any of five soils ranging from heavy clay to loamy sand (Grover and Smith, 1974). The dicamba degradation product, 3,6-dichlorosalicylic acid, adsorbed to sandy loam (30%), clay and silty clay (55%) (Smith, 1973a,b; Smith and Cullimore, 1975).

- Losses of 12 to 19% of the applied radioactivity from nonsterile soils indicated that metabolism contributes substantially more to ^{14}C-dicamba losses than does volatilization (Burnside and Levy, 1965; 1966).

- Under field conditions, dicamba (acid or salt form not specified) had half-lives of 1 to 2 weeks in a clay and a sandy loam soil when applied at 0.27 and 0.53 lb/acre (A). At either application rate, less than 30 ppb of dicamba remained after 4 weeks (Scifres and Allen, 1973). In another study, using a nonspecific bioassay method of analysis, dicamba phytotoxic residues dissipated within 2 years in loam and silty clay loam (Burnside et al., 1971).

- Ditchbank field studies indicated vertical movement of dicamba in soil; the soil layers at 6 to 12 inches contained a maximum of 0.07 ppm and 0.28 ppm in canals treated at 0.66 and 1.25 lb/A, respectively (Salman et al., 1972).

III. PHARMACOKINETICS

Absorption

- Atallah and Yu (1980) reported that mice, rats, rabbits and dogs administered single oral doses of ^{14}C-dicamba (99% purity, approximately 100 mg/kg) excreted an average of 85% of the administered dose in urine, as the parent compound, in 48 hours after dosing.

- Similar findings were reported for rats by Tye and Engel (1967) (96% excreted in 24 hours) and by Whitacre and Diaz (1976) (83% excreted unchanged in 24 hours). The data indicate that dicamba is rapidly absorbed from the gastrointestinal tract.

Distribution

- The retention of dicamba (99% purity, approximately 100 mg/kg) was investigated in rats, mice, rabbits and dogs following single doses by oral intubation (Atallah and Yu, 1980). They found that tissue levels were low and that dicamba did not accumulate in mammalian tissues.

- Tye and Engel (1967) also found low levels of dicamba in kidneys, liver and blood. These data also indicate that dicamba does not accumulate.

Metabolism

- The metabolism of ^{14}C-dicamba (99% purity) was investigated in mice, rats, rabbits and dogs after administration of approximately 100 mg/kg *per os* (Atallah and Yu, 1980). Between 90 to 99% of the dicamba was recovered unchanged in the urine of all four species. 3,6-Dichloro-2-hydroxybenzoic acid (DCHBA, a metabolite) was not detected in any urine sample at a level greater than 1% of the dose. There was also a small amount of unknown metabolites totaling about 1%.

Excretion

- Atallah and Yu (1980) investigated the excretion of ^{14}C-dicamba (99% purity) after a single oral dose (approximately 100 mg/kg) in mice rats, dogs and rabbits, and reported that 67 to 93% of the administered dose was excreted in urine of the four species within 16 hours. The compound was found to a lesser degree in feces (0.5 to 9%) and various tissues (0.17 to 0.5%) 16 hours postdosing.

IV. HEALTH EFFECTS

Humans

- The Pesticide Incident Monitoring System data base revealed 10 incident reports involving humans from 1966 to March 1981 for dicamba alone (U.S. EPA, 1981). Six of the ten reported incidents involved spraying operations. No concentrations were specified.

Exposed workers developed muscle cramps, dyspnea, nausea, vomiting, skin rashes, loss of voice or swelling of cervical glands. Four additional incidences resulted in coughing and dizziness in one child involved in an undescribed agricultural incident. Three children who sucked mint leaves from a ditch bank previously sprayed with dicamba were asymptomatic.

Animals

Short-term Exposure

- Reported acute oral LD_{50} values for technical dicamba [85.8% active ingredient (ai)] range from 757 to 1,414 mg/kg (Witherup et al., 1962) in rats. The acute oral LD_{50} in mice has been reported to be >4,640 mg/kg (Witherup et al., 1962) and 316 mg/kg in hens (Roberts et al., 1983).

- An acute inhalation LC_{50} of >200 mg/L was reported in Spartan strain rats (Wazeter et al., 1973).

- The neurotoxic effects of dicamba in hens were studied by Roberts et al. (1983). Technical dicamba (86.82% ai) was administered per os (10 hens/dose) in doses of 0, 79, 158 or 316 mg/kg. Two groups of ten hens each were dosed at 316 mg/kg. The various groups were observed for 21 days following treatment. No signs of ataxia were observed at any dose level tested. Histopathological evaluation of nervous tissue from 13 hens treated at 316 mg/kg demonstrated sciatic nerve damage in 6 hens (46%). The authors attributed this alteration to prolonged recumbency (inability to stand) rather than a direct effect of dicamba. Based on the absence of delayed neurotoxicity and sciatic nerve damage, a NOAEL of 158 mg/kg is identified for this study.

- Rats (two/sex/dose) of the Charles River CD strain were fed diets containing 658 to 23,500 ppm of technical dicamba (85.8% ai) for up to three weeks (Witherup et al., 1962). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to about 32.9 to 1,175 mg/kg/day. No adverse effects on physical appearance, behavior, food consumption, body or organ weights, gross pathology or histopathology were reported. Based on this information, a NOAEL of 1,175 mg/kg/day (the highest dose tested) is identified.

Dermal/Ocular Effects

- Wazeter et al. (1974) reported an acute LD_{50} for technical Banvel (85.8% ai) of >2000 mg/kg in dermal studies on New Zealand White rabbits (administration vehicle not stated).

- Heenehan et al. (1978) studied the sensitization potential of technical dicamba (86.8% ai) in Hartley albino guinea pigs. The compound was applied as a 10% suspension to the shaved backs of guinea pigs (five/sex) for 6 hours three times per week for 3 weeks. Following nine sensitizing doses, two challenge doses were applied. Dicamba was judged to cause moderate dermal sensitization.

- Technical dicamba (86.8% ai) was applied to the shaved backs of New Zealand White rabbits (four/sex/dose) in doses of 0, 100, 500 or 2,500 mg/kg/day, 5 days per week for 3 weeks (Dean et al., 1979). Slight skin irritation was observed at 100 mg/kg, and moderate irritation at 500 mg/kg/day and above. No changes were observed in general appearance, behavior, body weight, organ weight, biochemistry, hematology or urinalysis.

- Thompson (1984) instilled single doses (0.1 g) of technical dicamba (purity not specified) into the conjunctival sacs of nine New Zealand rabbits; three eyes were washed and six were not washed. Dicamba was severely irritating and corrosive to both washed and unwashed eyes.

Long-term Exposure

- Laveglia et al. (1981) fed CD rats (20/sex/dose) technical dicamba (86.8% ai) in the diet for 13 weeks in doses of 0, 1,000, 5,000 or 10,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 50, 250 or 500 mg/kg/day. No compound-related effects were observed in general appearance, hematology, biochemistry or in urinalysis values, survival and gross pathology at any dose levels tested. However, there was a decrease in mean body weight for both sexes (6.3% in females and 7.5% in males) at 10,000 ppm (500 mg/kg/day). The decrease in body weight was lower ($p < 0.05$) at week 13 when compared to controls. At this dose, there was also a decrease ($p < 0.05$) in the wet weight of the kidney. In addition, an increase ($p < 0.01$) in liver weight, when expressed as % of body weight, was reported. A NOAEL of 5,000 ppm (250 mg/kg/day) can be identified for this study.

- Male Wistar rats (20/dose) were fed diets containing technical dicamba at 0, 31.6, 100, 316, 1,000 or 3,162 ppm (corresponding to doses of 0, 3.8, 12, 37.3, 119 or 364 mg/kg/day) for 15 weeks (Edson and Sanderson, 1965). Following treatment, general behavior, physical appearance, food consumption, organ weights, gross pathology and histopathology were evaluated. However, the authors presented data only for the evaluation of body and organ weights. Hematological, urinalysis or clinical chemistry studies were not reported. No adverse effects were observed in the parameters measured at 316 ppm (37 mg/kg/day) or less. Relative liver-to-body weight ratios increased (p value not specified) at 1,000 and 3,162 ppm (119 and 364 mg/kg/day). Based on these data, the authors identified a NOAEL of 316 ppm (37 mg/kg/day).

- Davis et al. (1962) fed beagle dogs (three/sex/dose) technical dicamba (90% ai) in the diet in doses of 0, 5, 25 or 50 ppm for 2 years. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 0.125, 0.625 or 1.25 mg/kg/day. No compound-related effects were observed on survival, food consumption, hematology, urinalysis and organ weights. Although a decrease in body weight was observed in males at 25 and 50 ppm and in females at 50 ppm, no individual data except for body weight were reported, and no statistical evaluations were made. The authors did not present data on gross pathology and histopathology was done only on the heart, lung, liver and kidney. Based on this marginal information, a NOAEL or LOAEL will not be identified.

- Sprague-Dawley rats (32/sex/dose) were fed technical dicamba (90% ai) in the diet for 2 years in doses of 0, 5, 50, 100, 250 or 500 ppm (Davis et al., 1962). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 0.25, 2.5, 5, 12.5 or 25 mg/kg/day. The authors reported no adverse effects upon survival, body weight, food consumption, organ weight, hematologic values or histology at the dose levels tested. Since no data were presented for evaluation of pharmacologic effects, gross pathology, urinalysis or clinical chemistry and incomplete histological data were presented, a NOAEL could not be determined for this study due to insufficient data.

- Dicamba (Technical Reference Standard, 86.8% ai) was administered for 1 year to male and female beagle dogs (4/sex/dose) in their diet at mean dosage levels of 0, 2, 11 or 52 mg/kg/day (Blair, 1986). There were no chemical-related changes in behavior, food consumption, body weight, clinical hematology, biochemistry or urinalysis. In addition, no compound-specific effects on gross or microscopic pathology were observed. Based upon these data, a NOAEL of 52 mg/kg/day can be identified.

Reproductive Effects

- Charles River CD rats (20 females or 10 males/dose) were fed diets containing technical dicamba (87.2% ai) in doses of 0, 5, 50, 100, 250 or 500 ppm through three generations (Witherup et al., 1966). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 0.25, 2.5, 5, 12.5 or 25 mg/kg/day. Fertility index, gestation index, viability index, lactation index and pup development were comparable in treated and control rats. A NOAEL of 500 ppm (25 mg/kg/day) was identified.

Developmental Effects

- Technical dicamba (87.7% ai) was administered per os to pregnant New Zealand White rabbits (23-27/dose) at doses of 0, 0.5, 1, 3, 10 or 20 mg/kg/day from days 6 through 18 of gestation (Wazeter et al., 1977). No maternal toxicity, fetotoxicity or teratogenic effects were observed at 1 and 3 mg/kg/day. There were slightly reduced fetal and maternal body weights and increased postimplantation losses in the 10 mg/kg/day dose group when compared to untreated controls. The author did not consider these differences to be significant and identified a developmental toxicity NOAEL of 10 mg/kg/day. However, the EPA/OPP identified a maternal and fetotoxic NOAEL of 3 mg/kg/day, based on a reduction in body weights and increased post-implantation losses at the highest dose.

- Pregnant albino rats (20-24/dose) were administered technical-grade dicamba by gavage at dose levels of 0, 64, 160 or 400 mg/kg/day on days 6 throught 19 of gestation (Smith et al., 1981). No maternal toxicity was observed up to 160 mg/kg/day. Dicamba-treated dams in the 400-mg/kg/day dosage group exhibited ataxia and reduced body weight gain; they consumed less food during the dosing period when compared with controls given vehicle alone ($p < 0.05$). No fetotoxicity or developmental effects were observed at the dose levels tested. Based on these findings, a NOAEL for maternal toxicity of 160 mg/kg/day is identified. The NOAEL for fetotoxic and developmental effects is 400 mg/kg/day (the highest dose tested).

Mutagenicity

- Moriya et al. (1983) reported that dicamba (up to 5,000 ug/plate) exhibited no mutagenic activity against *Salmonella typhimurium* (TA 98, TA 100, TA 1535, TA 1537 and TA 1538) or *Escherichia coli* (WP2 hcr) either with or without metabolic activation.

- An increased number of chromosomal aberrations ($p < 0.01$) were reported in mouse bone marrow cells exposed to 500 mg/kg dicamba (Kurinnyi et al., 1982). No other details were presented and the data was not presented in the English summary. Accordingly, the significance of this report is unknown.

Carcinogenicity

- Sprague-Dawley rats (32/sex/dose) were administered dicamba (90% ai) in the diet for two years at doses of 0, 5, 50, 100, 250 or 500 ppm (Davis et al., 1962). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 0.25, 2.5, 5, 12.5 or 25 mg/kg/day. The treated rats did not differ from the untreated control animals with respect to the incidence, types and time of appearance of tumors.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\underline{\quad}\ \text{L/day})} = \underline{\quad}\ \text{mg/L}\ (\underline{\quad}\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA and NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for dicamba. Accordingly, it is recommended that the Ten-day HA value of 0.3 mg/L (calculated below) for a 10 kg child be used at this time as a conservative estimate of the One-day HA.

Ten-day Health Advisory

The developmental toxicity study by Wazeter et al. (1977) has been selected to serve as the basis for the Ten-day HA value for dicamba. In this study, pregnant rabbits administered technical dicamba (87.7 % ai) by gastric intubation at dosage levels of 0, 0.5, 1, 3, 10 or 20 mg/kg/day from days 6 through 18 of gestation showed slightly reduced maternal body weights at 10 mg/kg/day. Similarly, fetal body weights were slightly reduced, and postimplantation losses were increased in the 10-mg/kg/day dose group. Based on these data, a maternal and fetal toxicity NOAEL of 3 mg/kg/day is identified.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(3 \text{ mg/kg/day})\ (10 \text{ kg})}{(1 \text{ L/day})\ (100)} = 0.3 \text{ mg/L } (300 \text{ ug/L})$$

where:

3 mg/kg/day = NOAEL, based on absence of body weight loss and post-implantation losses.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

No studies found in the available literature were suitable for determining a Longer-term HA value for dicamba. One 13-week rat study (Laveglia et al., 1981) and one 15-week rat study (Edson and Sanderson, 1965) reported NOAELs (250 mg/kg/day and 37 mg/kg/day, respectively) that were higher than the NOAEL (3 mg/kg/day) of the rabbit study (Wazeter et al., 1978) selected to derive the Ten-day HA value. It is therefore recommended that the Reference Dose (RfD) derived below in the calculation of the Lifetime HA (0.03 mg/kg/day) be used at this time as the basis for the Longer-term HA. As a result, the Longer-term HA for the 10-kg child is 0.3 mg/L (300 ug/L) and for the 70-kg adult is 1.0 mg/L (1,000 ug/L).

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Although the 1-year dog study by Blair (1986) identifies a NOAEL of 52 mg/kg/day, this NOAEL will not be used to calculate the RfD. This decision is based on the facts that the IRDC study did not address reproductive and developmental toxicity and that the study of Wazeter et al. (1977) identifies, according to EPA/OPP, a maternal and fetotoxic NOAEL of 3 mg/kg/day. Since the reproductive and developmental effects appear to be seen at the lower exposure levels and to protect against potential fetotoxic effects, the RfD will be calculated using the NOAEL of 3 mg/kg/day.

The Lifetime HA is derived from this NOAEL as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{3\ \text{mg/kg/day}}{(100)} = 0.03\ \text{mg/kg/day}$$

where:

3 mg/kg/day = NOAEL based on the absence of fetotoxic effects.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.03\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 1.0\ \text{mg/L}\ (1{,}000\ \text{ug/L})$$

where:

0.03 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.
2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (1.05 mg/L) (20%) = 0.2 mg/L (200 ug/L)

where:

1.05 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- One study on the carcinogenicity of dicamba in rats has been reported (Davis et al., 1962). Although it revealed no evidence of carcinogenicity, it is limited in scope.
- The International Agency for Research on Cancer has not evaluated the carcinogenicity of dicamba.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), dicamba is classified in Group D: not classified. This category is used for substances with inadequate evidence of carcinogenicity in animal studies.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The NAS (1977) has calculated an ADI of 0.00125 mg/kg/day based on a NOAEL of 1.25 mg/kg/day from a 2-year feeding study in dogs and an uncertainty factor of 1,000. Assuming a body weight of 70 kg and a 20% source contribution factor, they calculated a Suggested-No-Adverse-Reaction-Level (SNARL) of 0.009 mg/L.
- Residue tolerances from 0.05 to 40 ppm have been established for a variety of agricultural products (U.S. EPA, 1985).

VII. ANALYTICAL METHODS

- Analysis of dicamba is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated acid pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is acidified and the compounds are extracted with ethyl ether using a separatory funnel. The derivatives are hydrolysed with potassium hydroxide and extraneous organic material is removed by a solvent wash. After acidification, the acids are extracted and converted to their methyl esters using diazomethane as the derivatizing agent. Excess reagent is removed and the esters are determined by electron capture GC. This method has been validated in a single laboratory and estimated detection limits have been determined for the analytes in this method. The estimated detection limit for dicamba is 0.081 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate granular-activated carbon (GAC) adsorption to be a possible removal technique for dicamba.
- Whittaker et al. (1982) report that a reduction of pH from 7 to 3 increased the extent of dicamba GAC adsorption. No system performance was reported.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

1,3-DICHLOROPROPENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

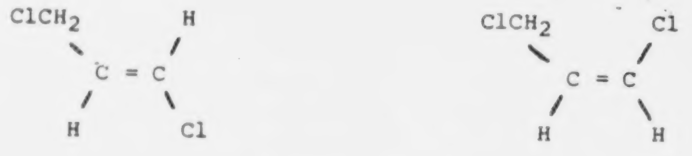
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 542-75-6

Structural Formula



(trans) (cis)

1,3-Dichloropropene
(approximately 46% trans/42% cis)

Synonyms

- Dichloro-1,3-propene; 1,3-dichloro-1-propene; cis/trans-1,3-dichloropropene; 1,3-D; DCP; D-D (approximately 28% cis/27% trans)

Uses

- DCP is the active ingredient in Telone*, a registered trademark of the Dow Chemical Company.
- The pesticide 1,3-dichloropropene (DCP) is a broad spectrum soil fumigant to control plant pests. Its major use is for nematode control on crops grown in sandy soils of the Eastern, Southern and Western U.S.
- The usage of DCP has increased due to cancellation of the once widely used product containing ethylene dibromide (EDB) and dibromochloropropane (DBCP) (U.S. EPA, 1986a).
- Estimated usage of DCP containing products in 1984 to 1985 ranged from about 34 to 40 million pounds (U.S. EPA, 1986a).

Properties (Dow Chemical USA, 1977, 1982; Clayton and Clayton, 1981)

Chemical Formula	$C_3H_4Cl_2$
Molecular Weight	110.98 (pure isomers)
Physical State (25°C)	Pale yellow to yellow liquid
Boiling Point	about 104°C (104.3°C, cis; 112°C, trans)
Density (25°C)	1.21 g/mL
Vapor Pressure (25°C)	27.3 mm Hg
Specific Gravity	about 1.2 (20/20°C)
Water Solubility (25°C)	0.1 to about 0.25% (1 to 2.5 g/L) reported; miscible with most organic solvents
Log Octanol/Water Partition Coefficient	25
Conversion Factor (25°C)(air)	1 mg/L = 220 ppm; 1 ppm = 4.54 mg/m^3

Occurrence

- In California (Maddy et al., 1982), 54 wells were examined in areas where Telone or D-D were used for several years. The well water did not have measurable amounts of DCP (<0.1 ppb).

- Monitoring data from New York have shown positive results for DCP in ground water (U.S. EPA, 1986b).

- In deep well sampling in southern California (65 to 1,200 foot depths), no DCP was detected. In shallow wells (3 to 4 meters) around potato fields in Suffolk County, NY, DCP was detected up to 138 days after application (OPP, 1988).

- DCP has been found in 41 of 1,088 surface water samples analyzed and in 10 of 3,949 ground water samples (STORET, 1988). Samples were collected in 800 surface water locations and 2,506 ground water locations; DCP was found in 13 states. The range of concentrations found in ground water was 0.2 ug/L to 90 ug/L. The 85th percentile of all non-zero samples was 1.3 ug/L in surface water and 3.4 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Available data indicate that DCP does leach to ground water. However, the relative hydrolytic instability of the parent compound would mitigate the potential for extensive contamination (U.S. EPA, 1986b; U.S. EPA, 1986c).

- The half-life of 1,3-DCP in soil was reported by Laskowski et al. (1982) to be approximately 10 days while Van Dijk (1974) reported 3 to 37 days depending on soil conditions and analytical methods.

- DCP hydrolyses as a function of temperature not as a function of pH. At 10°C, the half-life is 51 days while at 20°C it is 10 to 13 days. Chloroallyl alcohol is the main hydrolytic degradate. Some pholoysis of DCP does occur (OPP, 1988).

- In laboratory aerobic soil metabolism studies, DCP degrades to chloroallyl alcohol in 20 to 30 days where soil pH is between 5.0 and 7.0, the temperature is between 15 and 20°C and the organic matter content is from 1.5 to 11.6 percent in sandy loam or clay soils. In anaerobic soil metabolism studies, DCP degrades to chloroallyl alcohol to less than 8 percent in 30 days. For anaerobic aquatic metabolism studies, the half-life was reported to be about 20 days at pHs of 6.9 to 7.5 (OPP, 1988).

- In a field dissipation study done in the Netherlands, DCP (220-250 lb/A) injected into the soil at 9 to 19 cm depths was found to move rapidly downward over a 2 week period. In a similar study in Delano, CA, DCP was injected at 1,310 l/ha to 1,638 l/ha (=lb/A) to 81 cm. Samples at 14 days noted the presence of DCP (up to 0.5 ppm) at all depths to 8 feet (OPP, 1988).

III. PHARMACOKINETICS

Absorption

- Toxicity studies indicate that DCP is absorbed from skin, respiratory and gastrointestinal systems (Clayton and Clayton, 1981).
- Oral administration of DCP in rats resulted in approximately 90% absorption of the administered dose (Hutson et al., 1971).

Distribution

- Radiolabeled ^{14}C D-D (55% DCP) was administered orally in arachis oil in rats. After 4 days, most of the administered dose, based on measured radioactivity, was recovered primarily in urine and there were insignificant amounts (less than 5%) remaining in the gut, feces, skin and carcass (Hutson et al., 1971).

Metabolism

- cis-Dichloropropene in corn oil was given as a single oral dose (20 mg/kg bw) to two female Wistar rats. Urine and feces were collected separately. The main urinary metabolite (92%) was N-acetyl-S-[(cis)-3-chloroprop-2-enyl] cysteine. The cis-DCP has also been shown to react with glutathione in the presence of rat liver cystol to produce S[(cis)-3-chloroprop-2-enyl]glutathione. The cis-DCP is probably biotransformed to an intermediate glutathione conjugate and then follows the mercapturic acid pathway and is excreted in the urine as a cysteine derivitive (Climie and Morrison, 1978).
- In a study conducted by Dietz et al. (1984) rats and mice administered (via gavage) up to 50 and 100 mg DCP/kg bw, respectively, demonstrated no evidence of metabolic saturation.

Excretion

- In two studies (Hutson et al., 1971; Climie and Morrison, 1978) ^{14}C cis- and/or trans-DCP, administered orally in rats, were excreted primarily in the urine in 24 to 48 hours. When pulmonary excretion was evaluated (Hutson et al., 1971), the cis and trans isomers were 3.9% and 23.6% of the administered dose, respectively. Most of the cis-DCP was excreted in the urine.

IV. HEALTH EFFECTS

Humans

- The only known human fatality occurred a few hours after accidental ingestion of D-D mixture. The dosage was unknown. Symptoms were abdominal pain, vomiting, muscle twitching and pulmonary edema. Treatment by gastric lavage failed (Gosselin et al., 1976).

- Inhalation of DCP at high vapor concentrations resulted in gasping, refusal to breathe, coughing, substernal pain and extreme respiratory distress at vapor concentrations over 1,500 ppm (Gosselin et al., 1976).

- Venable et al. (1980) studied 64 male workers exposed to three carbon compounds including DCP to determine if fertility was adversely affected. The exposed study population was divided into ≤ 5 years exposure and >5 years exposure. Sperm counts and percent normal sperm forms were the major variables evaluated. Although the study participation rate for the exposed group was only 64%, no adverse effects on fertility were observed.

Animals

Short-term Exposure

- DCP is moderately toxic via single-dose oral administration. A technical product containing 92% cis-/trans-DCP was administered by gavage as a 10% solution in corn oil to rats. The oral LD_{50}s in male and female rats were 713 and 740 mg/kg, respectively (Torkelson and Oyen, 1977). In another study, the oral LD_{50} in the mouse for both males and females was 640 mg/kg (Toyoshima et al., 1978).

Dermal/Ocular Effects

- The percutaneous LD_{50}s for male and female mice dosed with DCP were greater than 1,211 mg/kg (Toyoshima et al., 1978).

- The percutaneous administration of DCP in rabbits (3 g/kg) resulted in mucous nasal discharge, depressed respiration and decreased body movements. The LD_{50} by this route was 2.1 g/kg (Torkelson and Oyen, 1977).

- Primary eye irritation and primary dermal irritation studies in rabbits indicated that DCP causes severe conjunctival irritation, moderate transient corneal injury and slight skin erythema/edema. Eye irritation was reversible 8 days post-instillation. The dermal LD_{50} in rabbits was 504 mg/kg (Dow, 1978).

Long-term Exposure

- Rats, guinea pigs, rabbits and dogs were exposed to 4.5 or 13.6 mg/m^3 DCP in air for 7 hours per day, and 5 days per week for 6 months.

The only effect noted was slight cloudy swelling of renal tubular epithelium in male rats exposed to the high dose (Torkelson and Oyen, 1977).

- Fischer 344 rats and CD-1 albino mice were exposed to Telone II (Production Grade) by inhalation exposure, 6 hours per day for 13 weeks at concentrations of 11.98, 32.14, or 93.02 ppm. Gross pathology revealed an increased incidence of kidney discoloration in the treated male rats relative to the control group. The significance of this lesion is unknown (Coate et al., 1979).

- Solutions of Telone (78.5% DCP) in propylene glycol were administered by gavage to 10 rats/sex/dose for six days per week for a period of 13 weeks. The dose levels were 1, 3, 10 or 30 mg/kg/day. The control groups were given propylene glycol. The daily administration of DCP to rats by stomach intubation up to a dosage of 30 mg/kg/day did not result in any major adverse effects. No significant effects on body weight, food consumption, hematology and histopathology were noted. However, at the 10 and 30 mg/kg/day doses, the relative weight of the kidney of males was higher than controls. The authors conclude that the no-toxic-effect level for DCP was between 3 and 10 mg/kg/day. The actual No-Observed-Adverse-Effect-Level (NOAEL) was 3 mg/kg/day (Til et al, 1973). This is the only study that can be used to develop a reference dose. However, because the design does not ideally address drinking water, a modifying factor will be used.

- The National Toxicology Program (NTP, 1985) evaluated the chronic toxicity and carcinogenicity of Telone II in rats and mice. These studies utilized Telone II fumigant containing approximately 89% cis- and trans-DCP. Groups of 52 male and female F344/N rats (doses 0, 25 or 50 mg/kg) and 50 male and female B6C3F$_1$ mice (doses 0, 50 or 100 mg/kg) were gavaged with Telone II in corn oil, 3 days per week up to 104 weeks. Ancillary studies were conducted [illegible] which dose groups containing five male and female rats were kil[illegible] after receiving Telone II for 9, 16, 21, 24 or 27 months. Toxic effects (noncarcinogenic) included basal cell or epithelial hyperplasia of the forestomach of rats and mice at all treatment levels of DCP. Epithelial hyperplasia of the urinary bladder of mice occurred at both treatment levels in males and females. Kidney hydronephrosis also occurred in mice. The study in male mice was considered inadequate due to the deaths of vehicle control animals. Many chronic toxicity parameters (hematology/ clinical chemistry) were not determined. The DCP used in the NTP study had a different stabilizer from the current Telone II.

- Scott et al. (1987) exposed groups of male and female B6C3F1 mice (70 animals/sex/exposure concentration) to vapors of Telone II* soil fumigant for 6 hours/day, 5 days/week for up to 24 months at 0, 5, 20 or 60 ppm. Urinary bladder effects including hyperplasia of bladder epithelium were noted in both sexes at 20 and 60 ppm. Hypertrophy and hyperplasia of the nasal respiratory mucosa were observed in most 60 ppm exposed mice of both sexes and in 20 ppm exposed females. Hyperplasia of the epithelial lining of the nonglandular portion of the stomach was observed in 60 ppm exposed males.

- Lomax et al. (1987) exposed groups of 70 male and female Fischer 344 rats to vapors of Telone II* soil fumigant for 6 hours/day, 5 days/week for up to 24 months at targeted concentrations of 0, 5, 20 or 60 ppm. The NOAEL was 20 ppm. The highest dose caused histopathological changes in nasal tissue as well as a decrease in body weight gain during the first year of this study. Males and females exposed to 60 ppm showed decreased thickness and erosions of the nasal epithelium as well as minimal submucosa fibrosis.

Reproductive Effects

- Groups of male and female Wistar rats were exposed to technical D-D at 0, 64, 145 and 443 mg/m^3 (0, 14, 12 or 94 ppm) for 5 days per week over 10 weeks. Male mating indices, fertility indices and reproductive indices were not affected by D-D exposure. No gross morphological changes were seen in sperm. Female mating, fertility and other reproductive indices were normal. Litter sizes and weights were normal and pup survival over 4 days was not influenced by exposure (Clark et al., 1980).

- Breslin et al. (1987) exposed by inhalation groups (F_0) of 30 males and 40 females for 10 weeks, 6 hours/day, 5 days/week to Telone II* at concentrations of 0, 10, 30 and 90 ppm prior to breeding. Exposure was increased to 7 days/week during breeding at weeks 11 to 13. Exposure of F_1 male and female parents to Telone II* began after weaning (approximately week 32 of the study) and continued for 12 weeks (5 days/week and 6 hours/day). The NOAEL for reproductive effects in the study was ≥90 ppm, the highest dose tested. Conception indices of females were somewhat reduced in the F_1 and F_2 generations. At 90 ppm, both males and females developed hyperplasia of respiratory epithelium and focal degeneration of olefactory tissue. Decreased body weight was observed in males and females exposed to 90 ppm.

Developmental Effects

- Hanley et al. (1987) investigated the effects of inhalation exposure to DCP on fetal development in rats. Pregnant Fischer 344 rats were exposed to 0, 20, 60 and 120 ppm DCP for 6 hr/day during gestation days 6 to 15. Maternal body weight gain was depressed in all of the DCP-exposed rats in a dose-related manner. Therefore, the Lowest-Observed-Adverse-Effect Level (LOAEL) for this effect was 20 ppm DCP. There was also significant depression of feed consumption in all exposed rats, along with decreases in water consumption in rats exposed to 120 ppm DCP. At 120 ppm there were significant increases in relative kidney weights and decreases in absolute liver weights in all exposed rats. There was a statistical increase in the incidence of delayed ossification of the vertebral centra of rats exposed to 120 ppm DCP. This effect is of little toxicological significance due to maternal toxicity observed at 120 ppm DCP.

- Hanley et al. (1987) also studied the effects of inhalation exposure to DCP on fetal development in rabbits. Pregnant New Zealand White rabbits were exposed to 0, 20, 60 or 120 ppm DCP for 6 hr/day during gestation days 6 through 18. In rabbits, evaluation of maternal weight gain over the entire exposure period indicated significant exposure-related decreases in both the 60- and 120-ppm groups. Therefore, the NOAEL was 20 ppm DCP. Statistically significant decreases in the incidence of delayed ossification of the hyoid and presence of cervical spurs among the exposed group were considered within normal variability in rabbits.

Mutagenicity

- Tests of commercial formulations containing DCP (DeLorenzo et al., 1975; Flessel, 1977; Neudecker et al., 1977; Brooks et al., 1978; Sudo et al., 1978; Stolzenberg and Hine, 1980), a mixture of pure cis-DCP and trans-DCP (DeLorenzo et al., 1975), and pure cis-DCP (Brooks et al, 1978) were positive in the Salmonella typhimurium strains TA1535 and TA100 with and without metabolic activation. These results indicate that DCP acts by base-pair substitution and is a direct acting mutagen.

- DCP may be a mutagen that acts via frame shift mutation since studies by DeLorenzo et al. (1975) reported positive results in TA1978 (with and without metabolic activation) for a commercial mixture of DCP and a mixture of pure cis- and trans-DCP.

- A commercial mixture of DCP and pure cis-DCP were also positive with and without metabolic activation in Salmonella typhimurium strain TA98 (Flessel, 1977; Sudo et al., 1978; Brooks et al., 1978).

- Sudo et al. (1978) tested DCP in a reverse mutation assay with E. coli B/r Wp2 with negative results.

- DCP was negative for reverse mutation in the mouse host-mediated test with S. typhimurium G46 in studies by Shirasu et al. (1976) and Sudo et al. (1978).

Carcinogenicity

- F344 rats of each sex were gavaged with Telone II in corn oil at doses of 0, 25 and 50 mg/kg/day for 3 days per week. A total of 77 rats/sex were used for each dose group (52 animals/sex/group were dosed for 104 weeks in the main oncogenicity study, and an ancillary study where 5 animals/sex/ group were sacrificed after 9, 16, 21, 24 and 27 months' exposure to DCP). No increased mortality occurred in treated animals. Neoplastic lesions associated with Telone II included squamous cell papillomas of the forestomach (male rats: 1/52; 1/52; 9/52; female rats: 0/52; 2/52; 3/52), squamous cell carcinomas of the forestomach (male rats: 0/52; 0/52; 4/52) and neoplastic nodules of the liver (male rats: 1/52; 6/52; 7/52). The increased incidence of forestomach tumors was accompanied by a positive trend for forestomach basal cell hyperplasia in male and female rats of both treated groups (25 and 50 mg/kg/day). The highest dose level tested in rats (50 mg/kg/day) approximated a maximum tolerated dose level (NTP, 1985).

- $B6C3F_1$ mice of each sex were gavaged with Telone II in corn oil at doses of 0, 50 and 100 mg/kg/day for 104 weeks. A total of 50 mice/sex were used for eacn dose group. Due to excessive mortality in control male mice from myocardial inflammation approximately 1 year after the initiation of the study, conclusions pertaining to oncogenicity were based on concurrent control data and NTP historical control data. Neoplastic lesions associated with the administration of Telone II included squamous cell papillomas of the forestomach (female mice: 0/50; 1/50; 2/50), squamous cell carcinomas of the forestomach (female mice: 0/50; 0/50; 2/50), transitional cell carcinomas of the urinary bladder (female mice: 0/50; 8/50; 21/48), and alveolar/bronchiolar adenomas (female mice: 0/50; 3/50; 8/50). The increased incidence of forestomach tumors was accompanied by an increased incidence of stomach epithelial cell hyperplasia in males and females at the highest dose level tested (100 mg/kg/day), and the increased incidence of urinary bladder transitional cell carcinoma was accompanied by a positive trend for bladder hyperplasia in male and female mice of both treated groups (50 and 100 mg/kg/day). Incidences of neoplasms were not significantly increased in male mice (NTP, 1985).

- Thirty female Ha:ICR Swiss mice received weekly subcutaneous injections of cis-DCP. The dose was 3 mg DCP/mouse in 0.05 mL trioctanoin delivered to the left flank. After 77 weeks, there was an increased incidence of fibrosarcomas at the site of injection. Six of the 30 exposed mice developed the tumors. There were no similar lesions in the controls (Van Duuren, 1979).

- Scott et al. (1987) exposed groups of male and female B6C3F1 mice (70 animals/sex/dose) to vapors of Telone II* for 6 hours/day, 5 days/week for up to 24 months at 0, 5, 20 or 60 ppm. The only tumorigenic effect was an increased incidence in benign lung tumors (bronchiolo-alveolar adenomas) in the 60 ppm exposed males. There were no tumorigenic effects in the lower-dose males or at any of the doses in females.

- Lomax et al. (1987) exposed Fisher 344 rats (70 rats/sex/dose) to vapors of Telone II* (0, 5, 20 and 60 ppm). The two year exposure by inhalation did not result in increases in tumor incidence.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

There are not sufficient data to derive a One-day Health Advisory value for DCP. It is recommended that the Longer-term HA value for a 10-kg child (30 ug/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

There are not sufficient data to derive a Ten-day HA value for DCP. It is recommended that the Longer-term HA value for a 10-kg child (30 ug/L, calculated below) be used as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The Til et al. (1973) 13 weeks subchronic gavage study in rats has been selected to serve as the basis for calculating the Longer-term HA for DCP. This study resulted in a LOAEL of 10.0 mg/kg/day based on increased relative kidney weight in males. No adverse effects were noted at the next lowest dose (3.0 mg/kg/day). Therefore, the NOAEL is 3.0 mg/kg/day.

Based on the NOAEL of 3.0 mg/kg/day determined in this study, the Longer-term HAs are calculated as follows:

For a 10-kg child:

$$\text{Longer-term HA} = \frac{(3.0\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (10)\ (1\ \text{L/day})} = 0.03\ \text{mg/L}\ (30\ \text{ug/L})$$

where:

3.0 mg/kg/day = NOAEL based on the absence of increased relative kidney weights in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

10 = modifying factor, selected since this was the only useful gavage study available and classified as supplementary data. Also there were considerable toxicological data gaps.

1 L/day = assumed daily water consumption of a child.

For a 70-kg adult:

$$\text{Longer-term HA} = \frac{(3.0\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (10)\ (2\ \text{L/day})} = 0.105\ \text{mg/L}\ (100\ \text{ug/L})$$

where:

3.0 mg/kg/day = NOAEL based on the absence of increased relative kidney weights in rats.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

10 = modifying factor, selected since this was the only useful gavage study available and classified as supplementary data. Also there were considerable toxicological data gaps.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (e.g., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential, then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical. For Group C carcinogens, an additional safety factor of 10 is added to the DWEL.

The Lifetime HA for a 70-kg adult has been determined on the basis of the study in rats by Til et al. (1973), as described above.

Using the NOAEL of 3.0 mg/kg/day, as determined in that study, the DWEL is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(3.0\ \text{mg/kg/day})}{(1{,}000)\ (10)} = 0.0003\ \text{mg/kg/day}$$

where:

3.0 mg/kg/day = NOAEL based on the absence of increased relative kidney weights in rats.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

10 = modifying factor selected since this was the only useful gavage study available and classified as supplementary data. Also there were considerable toxicological data gaps.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.0003\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = .011\ \text{mg/L}\ (10\ \text{ug/L})$$

where:

0.0003 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HAs are not recommended for Group A or B carcinogens. DCP is a Group B2, probable human carcinogen. The estimated cancer risk associated with lifetime exposure to drinking water containing DCP at 10 ug/L is approximately 5.0×10^{-5}. This estimate represents the upper 95% confidence limit using the linearized multistage model. The actual risk is unlikely to exceed this value.

Evaluation of Carcinogenic Potential

- DCP may be classified as a B2, probable human carcinogen based on sufficient evidence of tumor production in two rodent species and two routes of administration.

- Data on an increased incidence of squamous cell papilloma or carcinoma of the forestomach in rats exposed to DCP (NCI, 1985) were used for a quantitative assessment of cancer risk due to DCP. Based on the data from this study and using the linearized multistage model, a carcinogenic potency factor (q_1^*) for humans of 1.75×10^{-1} $(\text{mg/kg/day})^{-1}$ was calculated.

- The drinking water concentrations corresponding to increased lifetime cancer risks of 10^{-4}, 10^{-5} and 10^{-6} (one excess cancer per one million population) for a 70-kg adult consuming 2 L/day are 20 ug/L, 2 ug/L and 0.2 ug/L, respectively.

- The forestomach tumor data in male rats used to calculate the q_1^* value (NCI, 1985) consisted of the 2-year study data excluding the ancillary studies data. The ancilliary studies involved serial sacrifice of animals (at 9, 16, 21, 24 and 27 months). It is not appropriate to include these data in the lifetime predictive model used (multistage).

- For comparison purposes, drinking water concentrations associated with an excess risk of 10^{-6} were 0.2 ug/L, 3.6 mg/L, 0.03 ug/L and 0.004 ug/L for the one-hit, Weibull, probit and logit models, respectively.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The ACGIH recommended 1 ppm (5 mg/m^3) as a Threshold Limit Value for DCP (Clayton and Clayton, 1981).

VII. ANALYTICAL METHODS

- No specific methods have been published by U.S. EPA for analysis of DCP in water. However, EPA Method 524.2 (U.S. EPA, 1986d) and EPA Method 502.2 (USEPA, 1986e) both for volatile organic compounds in water should be suitable for analysis of DCP. Both are standard purge and trap capillary column gas chromatographic techniques. While an estimated detection limit has not been calculated for the two isomers of 1,3-dichloropropene, work done with 1,1-dichloropropene would indicate a range for 1,3-DCP of 0.02 to 0.05 ug/L.

VIII. TREATMENT TECHNOLOGIES

- There are no specific publications on treatment of 1,3-DCP. However, adequate treatment by granular activated carbon (GAC) should be possible. Freundlich carbon absorption isotherms for DCP indicate reasonably high adsorption capacity (U.S. EPA, 1980).

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

DIELDRIN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

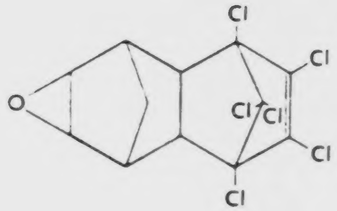
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 60-57-1

Structural Formula



Dieldrin; 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7:3,6-dimethanonaphth[2,3-b]oxirene (Windholz, 1983).

Synonyms

- HEOD; Alvit; Quintox; Octalox (IPCS, 1987).

Uses

- Formerly used for control of soil insects, public health insects, termites and many other pests. These uses have been cancelled and manufacture discontinued in the United States (Meister, 1983).

Properties (NAS, 1977; Weast and Astle, 1982; Windholz, 1983)

Chemical Formula	$C_{12}H_8Cl_6O$
Molecular Weight	380.93
Physical State	Crystals
Boiling Point	--
Melting Point	175 to 176°C
Density	--
Vapor pressure (20°C)	3.1×10^{-6} mm Hg
Water Solubility (25°C)	0.25 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold (water)	0.04 mg/L
Conversion Factor	--

Occurrence

- Dieldrin has been found in 7,320 of 50,473 surface water samples analyzed and in 223 of 5,443 ground water samples (STORET, 1988). Samples were collected at 9,021 surface water locations and 4,131 ground water locations, and Dieldrin was found in 48 states, Canada and Puerto Rico. The 85th percentile of all nonzero samples was 0.01 ug/L in surface water and 0.10 ug/L in ground water sources. The maximum concentration found was 301 ug/L in surface water and in 10.08 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Dieldrin is stable and highly persistent in the environment.

- Dieldrin has the longest half-life of the chlorinated hydrocarbons in water 1-m deep (half-life = 723 days) (MacKay and Wolkoff, 1973).

III. PHARMACOKINETICS

Absorption

- A single oral dose of dieldrin at 10 mg/kg body weight (bw) administered in corn oil to male Sprague-Dawley rats produced consistent concentrations of dieldrin in plasma, muscle, brain, kidney and liver for periods up to 48 hours (Hayes, 1974); hence, it was absorbed.

Distribution

- Rats given a single oral dose of dieldrin at 10 mg/kg showed concentrations of dieldrin in fat, muscle, liver, blood, brain and kidney. The highest concentration of dieldrin was in fat. The lowest concentration was in the kidney (Hayes, 1974).

Metabolism

- Both the CFE rat and CF1 mouse, following a single oral dose of dieldrin (not less than 85% HEOD) at 3 and 10 mg/kg in olive oil, respectively, metabolized dieldrin to 9-hydroxydieldrin, 6,7-trans-dihydroaldrindiol and some unidentified metabolites. The rat, but not the mouse, also metabolized dieldrin to pentachloroketone (Baldwin and Robinson, 1972).

Excretion

- Female rats infused with total doses of 8 to 16 mg ^{36}Cl-dieldrin/kg bw excreted approximately 70% of the infused dose in the feces over a period of 42 days, while only about 10% of the dose was recovered in the urine. Excretion was markedly increased by restriction of the diet indicating that the concentration of dieldrin in the blood increased as fat was mobilized (Heath and Vandekar, 1964).

IV. HEALTH EFFECTS

Humans

- Dieldrin has been reported to cause hypersensitivity and muscular fasciculations that may be followed by convulsive seizures and respective changes in the EEG pattern. Acute symptoms of intoxication include hyperirritability, convulsions and/or coma sometimes accompanied by nausea, vomiting and headache, while chronic intoxication may result in fainting, muscle spasms, tremors and loss of weight. The lethal dose for humans is estimated to be about 5 g (ACGIH, 1984).

Animals

Short-term Exposure

- RTECS (1985) reported the acute oral LD_{50} values of dieldrin in the rat, mouse, dog, monkey, rabbit, pig, guinea pig and hamster as 38.3, 38, 65, 3, 45, 38, 49 and 60 mg/kg, respectively.

Dermal/Ocular Effects

- Aldrin or Dieldrin (dry powder) applied to rabbit skin for 2 h/day, 5 days/week for 10 weeks had no discernible effects (IPCS, 1987).

Long-term Exposure

- Groups of Osborne-Mendel rats, 12/sex/level, were fed 0, 0.5, 2, 10, 50, 100 or 150 ppm dieldrin (recrystallized, 100% active ingredient) in their diet for 2 years. These doses correspond to approximately 0, 0.025, 0.1, 0.5, 2.5, 5.0 or 7.5 mg/kg/day, respectively (Lehman, 1959). Survival was markedly decreased at levels of 50 ppm and above. Liver-to-body weight ratios were significantly increased at all treatment levels, with females showing the effect at 0.5 ppm and males at 10 ppm and greater. Microscopic lesions were described as being characteristic of chlorinated hydrocarbon exposure. These changes were minimal at the 0.5 ppm level. Male rats, at the two highest dose levels (100 and 150 ppm), developed hemorrhagic and/or distended urinary bladders usually associated with considerable nephritis (Fitzhugh et al., 1964). A Lowest-Observed-Adverse-Effect-Level (LOAEL) of 0.025 mg/kg/day, the lowest dose tested, was identified in this study.

- Mongrel dogs, one/sex/dose level (two/sex at 0.5 mg/kg/day), fed dieldrin (recrystallized, 100% active ingredient) at 0.2 to 10 mg/kg/day, 6 days/week for up to 25 months, showed toxic effects including weight loss and convulsions at dosages of 0.5 mg/kg/day or more. Survival was inversely proportional to dose level. No toxic effects, gross or microscopic, were seen at a dose level of 0.2 mg/kg/day (Fitzhugh et al., 1964).

- Groups of Carworth Farm "E" strain rats, 25/sex/dose level, were fed dieldrin (>99% purity) in the diet at 0.0, 0.1, 1.0 or 10.0 ppm for

2 years. These doses correspond to approximately 0, 0.005, 0.05 or 0.5 mg/kg/day, respectively (Lehman, 1959) At 7 months, the 1-ppm intake level was equivalent to approximately 0.05 and 0.06 mg/kg/day for males and females, respectively. No effects on mortality, body weight, food intake, hematology and blood or urine chemistries were seen. At the 10-ppm level, all animals became irritable after 8 to 13 weeks of treatment and developed tremors and occasional convulsions. Liver weight and liver-to-body weight ratios were significantly increased in females receiving both 1.0 and 10 ppm. Pathological findings described as organochlorine-insecticide changes of the liver were found in one male and six females at the 10-ppm level. No evidence of tumorigenesis was found (Walker et al., 1969).

- Groups of beagle dogs (five/sex/dose) were treated daily by capsule with dieldrin (>99% purity) at 0.0, 0.005 or 0.05 mg/kg in olive oil for 2 years. No treatment-related effects were seen in general health, behavior, body weight or urine chemistry. A significant increase in plasma alkaline phosphatase activity in both sexes and a significant decrease in serum protein concentration in males receiving the high dose were not associated with any clinical or pathological change. Liver weight and liver-to-body weight ratios were significantly increased in females receiving the high dose, 0.05 mg/kg/day, but no gross or microscopic lesions were found. There was no evidence of tumorigenic activity (Walker et al., 1969).

- Dieldrin (>99% pure) was administered to CF1 mice of both sexes (30/sex/dose) in the diet for 128 weeks. Dosages were 1.25, 2.5, 5, 10 or 20 ppm dieldrin. These doses are equivalent to 0.19, 0.38, 0.75, 1.5 or 3 mg/kg body weight (Lehman, 1959). At the 20-ppm dose level, approximately 25% of the males and nearly 50% of the females died during the first 3 months of the experiment. Palpable intra-abdominal masses were detected after 40, 75 or 100 weeks in the 10, 5 and 2.5-ppm-treated groups, respectively. At 1.25 ppm, liver enlargement was not palpable and morbidity was similar to that of controls. A No-Observed-Adverse-Effect-Level (NOAEL) cannot be established because clinical chemistry parameters were not determined (Walker et al., 1972).

Reproductive Effects

- Coulston et al. (1980) studied the reproductive effects of dieldrin in Long Evans rats. Pregnant rats (18-20/dose) were administered 0 or 4 mg/kg bw dieldrin by gavage daily from day 15 of gestation through 21 days postpartum. The treated group did not differ from the control group when examined for fecundity, number of stillbirths, perinatal mortality and total litter weights.

Developmental Effects

- Pregnant Syrian golden hamsters given 30 mg/kg bw dieldrin (≥99% pure) in corn oil on days 7, 8 or 9 of gestation manifested an embryocidal and teratogenic response as evidenced by a statistically significant increase in fetal deaths, a decrease in live fetal weight and an increased incidence of webbed foot, cleft palate and open eye (Ottolenghi et al., 1974). Similar anomalies were observed in CD_1 mice administered 15 mg/kg bw dieldrin on day 9 of gestation, but no effect was seen on fetal survival or weight.

- Dieldrin (87% pure) was not found to be teratogenic in the CD rats and CD-1 mice administered doses of 1.5, 3.0 or 6.0 mg/kg/day by gastric intubation on days 7 through 16 of gestation. Fetal toxicity, as indicated by a significant decrease in numbers of caudal ossification centers at the 6.0-mg/kg/day dose level and a significant increase in the number of supernumerary ribs in one study group at both the 3.0- and 6.0-mg/kg/day dose level, was reported in the experiments in mice. Maternal toxicity in the high-dose rats was indicated by a 41% mortality and a significant decrease in weight gain; similarly, mice receiving 6.0 mg/kg/day showed a significant decrease in maternal weight gain. A significant increase in liver-to-body weight ratio in one group of maternal mice was reported at both 3.0 and 6.0 mg/kg/day (Chernoff et al., 1975).

Mutagenicity

- Dieldrin was not mutagenic in the *Salmonella*/microsome test with and without S-9 mix (McCann et al., 1975).

- Dieldrin significantly decreased the mitotic index and increased chromosome abnormalities in STS mice bone marrow cells in an *in vivo* study. Similar observations were made in human WI-38 embryonic lung cells in an *in vitro* test that also gave evidence of cytotoxicity, as indicated by degree of cell degeneration (Majumdar et al., 1976).

Carcinogenicity

- A dose-related increase in the incidence of hepatocellular carcinomas was observed in $B6C3F_1$ mice, with the incidence in the high-dose males being significantly ($p = 0.025$) higher when compared to pooled controls (NCI, 1978). Mice were given dieldrin (technical grade, >85% purity) in the diet at concentrations of 2.5 or 5 ppm for 80 weeks. These doses correspond to approximately 0.375 or 0.75 mg/kg/day, respectively (Lehman, 1959).

- Osborne-Mendel rats treated with dieldrin at Time-Weighted Average (TWA) doses of 29 or 65 ppm in the diet (approximately 1.45 or 3.25 mg/kg/day, respectively, based on Lehman, 1959) for 80 weeks, did not elicit treatment-related tumors (NCI, 1978).

- Diets containing 0.1, 1.0 or 10 ppm dieldrin (>99% purity), when given to mice of both sexes for 132 weeks, were associated with an increased incidence of liver tumors at all dose levels tested (Walker et al., 1972). These doses are equivalent to approximately 0.015, 0.15 or 1.5 mg/kg/day, respectively (Lehman, 1959).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were found in the available literature that was suitable for determination of a One-day HA value for dieldrin. It is, therefore, recommended that the modified DWEL for a 10-kg child (0.0005 mg/L) be used as a conservative estimate for the One-day HA value.

Ten-day Health Advisory

No data were found in the available literature that was suitable for determination of a Ten-day HA value for dieldrin. It is, therefore, recommended that the modified DWEL for a 10-kg child (0.0005 mg/L) be used as a conservative estimate for the Ten-day HA value.

Longer-term Health Advisory

No data were found in the available literature that was suitable for determination of a Longer-term HA value for dieldrin. It is, therefore, recommended that the modified DWEL for a 10-kg child (0.0005 mg/L) be used as a conservative estimate for the Longer-term HA value.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study of Walker et al. (1969), in which rats were fed dieldrin in the diet at 0.0, 0.1, 1 or 10 ppm for 2 years (approximately 0, 0.005, 0.05 or 0.5 mg/kg/day based on Lehman, 1959), has been selected as the basis for calculating the DWEL. In this study, liver weight and liver-to-body weight ratios were significantly increased in females receiving 1 and 10 ppm, while pathological changes consistent with exposure to organochlorides were evident at the 10-ppm level. This study established a NOAEL of 0.1 ppm (equivalent to 0.005 mg/kg/day).

Using a NOAEL of 0.005 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{0.005 \text{ mg/kg/day}}{100} = 0.00005 \text{ mg/kg/day}$$

where:

0.005 mg/kg/day = NOAEL, based on the absence of hepatic effects in rats fed dieldrin in the diet.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent (DWEL)

$$\text{DWEL} = \frac{(0.00005 \text{ mg/kg/day})(70 \text{ kg})}{2 \text{ L/day}} = 0.00175 \text{ mg/L } (2 \text{ ug/L})$$

where:

0.00005 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Dieldrin may be classified in Group B2: probable human carcinogen. A Lifetime HA is not recommended for dieldrin.

The estimated excess cancer risk associated with lifetime exposure to drinking water containing dieldrin at 1.75 ug/L is approximately 8.05 x 10^{-4}. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group (U.S. EPA, 1987) using the linearized multistage model. The actual risk is unlikely to exceed this value.

Evaluation of Carcinogenic Potential

- Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), dieldrin may be classified in Group B2: probable human carcinogen.
- Evidence has been presented in several carcinogenicity studies showing that dieldrin is carcinogenic to mice. Thirteen data sets from these studies are adequate for quantitative risk estimation. Utilizing the linearized multistage model, the U.S. EPA performed potency estimates for each of these data sets. The geometric mean of the potency estimates, $q_1^* = 16$ $(mg/kg/day)^{-1}$, was estimated as the potency for the general population (U.S. EPA, 1987).
- Using this q_1^* value and assuming that a 70-kg human adult consumes 2 liters of water a day over a 70-year lifespan, the linearized multistage model estimates that concentrations of 0.219, 0.0219 and 0.00219 ug dieldrin per liter may result in excess cancer risk of 10^{-4}, 10^{-5} and 10^{-6}, respectively.
- The linearized multistage model is only one method of estimating carcinogenic risk. From the data contained in U.S. EPA (1987), it was determined that five of the thirteen data sets were suitable for determining slope estimates for the probit, logit, Weibull and gamma-multihit models. Using the geometric mean of these slope estimates (13 for multistage, 5 for other models) at their upper 95% confidence limits, the following comparisons of unit risk (i.e., a 70-kg man consuming 2 liters of water per day containing 1 ug/L of dieldrin over a lifetime) can be made: multistage, 4.78 x 10^{-4}; probit, 7.7 x 10^{-12}; logit, 5.09 x 10^{-6}; Weibull, 1.13 x 10^{-4}; multihit, 5.68 x 10^{-4}. Each model is based on different assumptions. No current understanding of the biological mechanisms of carcinogenesis is able to predict which of these models is more accurate than another.
- IARC (1982) concluded that there is limited evidence that dieldrin is carcinogenic in laboratory animals.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- ACGIH (1984) has established a short-term exposure limit (STEL) of 0.75 mg/m^3 and an 8-hour Threshold Limit Value (TLV)-TWA exposure 0.25 mg/m^3 for dieldrin.

- U.S. EPA (1980) has recommended ambient water quality criteria of 0.71 ng/L for dieldrin. It is based on a carcinogenic potency factor (q_1*) of 30.37 $(mg/kg/day)^{-1}$ derived from the incidence of hepatocellular carcinoma in a mouse feeding study conducted by Walker et al. (1972).

- Residue tolerances ranging from 0.02 to 0.1 ppm have been established for dieldrin in or on agricultural commodities (U.S. EPA, 1985).

- WHO (1982) established guidance of 0.03 ug dieldrin/L in drinking water.

VII. ANALYTICAL METHODS

- Determination of dieldrin is by Method 508, Determination of Chlorinated Pesticides in Water by Gas Chromatography with an Electron Capture Detector (U.S. EPA, 1988). In this procedure, a measured volume of sample of approximately 1 liter is solvent extracted with methylene chloride by mechanical shaking in a separatory funnel or mechanical tumbling in a bottle. The methylene chloride extract is isolated, dried and concentrated to a volume of 5 mL after solvent substitution with methyl tert-butyl ether (MTBE). Chromatographic conditions are described which permit the separation and measurement of the analytes in the extract by GC with an electron capture detector (ECD). This method has been validated in a single laboratory, and estimated detection limits have been determined for the analytes in the method, including dieldrin, that the estimated detection limit is 0.02 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that reverse osmosis (RO), granular-activated carbon (GAC) adsorption, ozonation and conventional treatment will remove dieldrin from water. The percent removal efficiency ranges from 50 to 99+%.

- Laboratory studies indicate that RO is a promising treatment method for dieldrin-contaminated waters. Chian et al. (1975) reported 99+% removal efficiency for two types of membranes operating at 600 psig and a flux rate of 8 to 12 gal/ft^2/day. Membrane adsorption, however, is a major concern and must be considered, since breakthrough of dieldrin would probably occur once the adsorption potential of the membrane was exhausted.

- GAC is effective for dieldrin removal. Pirbazari and Weber (1983) reported 99+% dieldrin removal efficiency of a GAC column operating at an empty bed contact time (EBCT) of 15 minutes and a hydraulic loading of 1.4 gal/ft^2/min, for the entire test period (approximately 7.5 months).

- Pirbazari and Weber (1983) determined adsorption isotherms using GAC on dieldrin in water solutions. Resin adsorption was also found to remove dieldrin from water. The Freundlich values determined by The authors indicate that the tested resins are not quite as effective as GAC in the removal of dieldrin from water.

- Ozonation treatment appears to be an effective dieldrin removal method. Treatment with 36 mg/L ozone (03) removed 50% of dieldrin while 11 mg/L 03 removed only 15% of dieldrin (Robeck et al., 1965).

- Conventional water-treatment techniques using alum coagulation, sedimentation and filtration proved to be 55% effective in removing dieldrin from contaminated potable water supplies (Robeck et al., 1965). Lime- and soda-ash softening with ferric chloride as a coagulant did not improve upon the removal efficiency achieved with alum alone.

- Oxidation with chlorine and potassium permanganate is ineffective in degrading dieldrin (Robeck et al., 1965).

- Treatment technologies for the removal of dieldrin from water are available and have been reported to be effective. However, selection of individual or combinations of technologies to attempt dieldrin removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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August, 1988

DIMETHRIN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

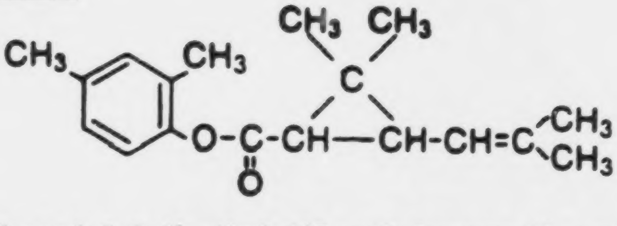
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 67239-16-1

Structural Formula



2,4-Dimethylbenzyl-2,2-dimethyl-3(2-methylpropenyl)-cyclopropane carboxylate

Synonyms

- ENT 21,170; Chrysanthemumic acid; 2,4-Dimethylbenzylester.

Uses

- Insecticide for use in ponds and swamps as a mosquito larvicide (Meister, 1986).

Properties

Chemical Formula	$C_{18}H_{24}O_2$
Molecular Weight	286.39 (Ambrose, 1964)
Physical State (25°C)	Amber liquid
Boiling Point	175°C
Melting Point	—
Density	—
Vapor Pressure (25°C)	—
Specific Gravity	0.98
Water Solubility (25°C)	Insoluble (further details not provided)
Log Octanol/Water Partition Coefficient	—
Taste Threshold	—
Odor Threshold	—
Conversion Factor	—

Occurrence

- No information is available on the occurrence of dimethrin in water.

Environmental Fate

- No information is available on the environmental fate of dimethrin.

III. PHARMACOKINETICS

Absorption

- In a preliminary metabolic study by Ambrose (1964), four rabbits were given 5 mL/kg (5 mg/kg) of undiluted dimethrin by intubation. Urine was collected every 24 hours over a 72-hour period. Identification of two possible metabolites in the urine indicated that dimethrin was absorbed. Sufficient data were not available to quantify the extent of absorption.

Distribution

- No information on the distribution of dimethrin was found in the available literature.

Metabolism/Excretion

- Information presented by Ambrose (1964) indicates that dimethrin (5 mg/kg), administered by intubation to rabbits, is metabolized (by reduction) and excreted in the urine as chrysanthemumic acid and the glucuronic ester of 2,4-dimethyl benzoic acid. Sufficient information was not presented to determine if these are the only metabolites of dimethrin or if any unchanged dimethrin is excreted.

IV. HEALTH EFFECTS

Humans

- No information on the health effects of dimethrin in humans was found in the available literature.

Animals

Short-term Exposure

- The acute oral LD_{50} value of dimethrin for male and female Sherman rats was reported to be >15,000 mg/kg (Gaines, 1969).

- Ambrose (1964) conducted an acute oral study in which male and female albino rabbits (two/sex/dose) and male albino Wistar-CWL rats (five/dose) were given a single dose of 10 or 15 mL/kg (9.8 or 14.7 mg/kg) of technical-grade dimethrin (98% pure) by gavage. Albino guinea pigs (four/sex) received a single dose of 10 mL/kg (9.8 mg/kg) by gavage. No effects were observed in rats or rabbits during a 2-week observation period. (Specific parameters observed were not identified). In guinea pigs, the only effect reported during a similar observation period was a refusal to eat or drink for 24 hours following dosing.

- Ambrose (1964) administered 10 mL/kg (9.8 mg/kg) of technical-grade dimethrin (98% pure) to 15 male albino Wistar-CWL rats by gavage, 5 days per week for 3 weeks. This corresponds to an average daily dose of 7 mg/kg. No adverse effects, as judged by general appearance, behavior and growth, were observed. At necropsy, no gross abnormalities were observed. No histopathological examinations were performed.

Dermal/Ocular Effects

- Ambrose (1964) conducted a dermal irritation study in which dimethrin (98% pure) was applied at a dose level of 10 mL/kg (9.8 mg/kg) to the intact or abraded skin of four albino rabbits (two/sex) for a 24-hour exposure period. No skin irritation was observed immediately after the removal of the dimethrin or during a 2-week observation period.

- Ambrose (1964) reported that single or multiple (3 consecutive days) instillations of 0.1 mL of undiluted dimethrin (98% pure) into the conjunctival sac of eight albino rabbits caused no visible irritation or chemosis and no injury to the cornea as detectable by means of fluorescein staining. When 0.2 mL of dimethrin was applied to the penile mucosa of five albino rabbits on two occasions 6 days apart, no irritation or sloughing of the mucosa was observed during a 1-week observation period.

- Masri et al. (1964) applied 3 mL of undiluted dimethrin to the shaved back and sides of three albino rabbits 10 times over a 2-week period (frequency of application not specified). The only reported reaction was the development of a slight scaliness which disappeared after cessation of application.

- Ambrose (1964) applied dimethrin (98% pure) to the skin of albino rabbits (five/dose) 5 days per week for 13 weeks (65 applications). Doses administered were 0.5 mL/kg undiluted dimethrin or 0.5 mL/kg of a 50% solution of dimethrin in cottonseed oil (equivalent to 0.25 mL/kg of dimethrin); controls received 0.5 mL/kg of cottonseed oil only. No evidence of any cutaneous reaction was observed. Occasionally, a slight, nonpersistent erythema was observed in all groups of rabbits. At necropsy, all organs from treated animals were indistinguishable from the controls. No histopathological differences between control and treated animals were observed.

Long-term Exposure

- Masri et al. (1964) administered dimethrin to male (five/dose) and female (six/dose) weanling albino rats for 16 weeks at dietary levels of 0, 0.2, 0.6, 1.5 or 3.0%. Based on food consumption and body weight data presented in the study, these dietary levels of dimethrin were calculated to correspond to about 0, 120, 320, 1,000 or 2,300 mg/kg/day for males, and 0, 130, 400, 1,100 or 2,500 mg/kg/day for females. Results indicated a significant reduction in body weight in males receiving 0.6 or 3.0% and females receiving 1.5 or 3.0%. Absolute liver weight and liver-to-body weight ratios were significantly higher in both the male and female 1.5- and 3.0%-dose groups. Kidney-to-body weight ratios were also significantly higher for these groups. Scattered gross pathologic changes did not appear to bear a relationship to dose. Histopathological examination revealed dose-related morphological changes in the liver that consisted of a round eosinophilic ring in the cytoplasm, approximately the size of the nucleus. Amorphous material within the ring stained less densely than the rest of the cytoplasm. Also, many hepatic cells of rats receiving 1.5 or 3.0% dimethrin appeared larger than those of controls and had less distinct basophilic cytoplasmic particles. Hepatic changes were less pronounced in the 0.6% group. No cell inclusions were seen in rats receiving 0.2% dimethrin. The effects of increased liver and kidney-to-body weight ratios as well as histopathological changes in the liver were shown to be reversible after withdrawal of dimethrin. The No-Observed-Adverse-Effect Level (NOAEL) identified in this study was 0.2% dimethrin (120 mg/kg/day for males; 130 mg/kg/day for females).

- Ambrose (1964) administered dimethrin to male and female albino Wistar-CWL rats (10/sex/dose) for 52 weeks at dietary levels of 0, 0.05, 0.1, 0.5, 1.0 or 2.0%. These dietary levels correspond to 0, 30, 60, 300, 600 or 1200 mg/kg/day. The only statistically significant effect reported in this study was an increase in the liver-to-body weight ratios in both male and female animals receiving 1.0 or 2.0% dimethrin. Withdrawal of dimethrin from the diet for 6 weeks resulted in return of liver weights to levels indistinguishable from the controls. No differences in hemoglobin parameters were noted between the treated and control animals at any time during the 52-week period. Histologically, no significant changes or lesions that could be attributed to dimethrin in the diet were observed in any of the test groups of animals. A NOAEL of 300 mg/kg was identified from this study.
- As described in a review by Cohen and Grasso (1981), dimethrin has been implicated as a hypolipidemic agent and causes an increase in hepatic peroxisome proliferation . Dietary administration of certain hypolipidemic agents to rodents has resulted in the induction of liver carcinomas.

Reproductive Effects

- No information on the reproductive effects of dimethrin was found in the available literature.

Developmental Effects

- No information on the developmental effects of dimethrin was found in the available literature.

Mutagenicity

- No information on the mutagenicity of dimethrin was found in the available literature.

Carcinogenicity

- No information on the carcinogenicity of dimethrin was found in the available literature. However, the report by Cohen and Grasso (1981) implicating dimethrin as a hypolipidemic agent may indicate that dimethrin has carcinogenic potential in rodents. (It should be noted that the relationship between hypolipodemic agents and liver carcinomas in rodents has not been observed in humans.)

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA values for dimethrin. It is therefore recommended that the Longer-term HA for a 10-kg child (10 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

No information was found in the available literature that was suitable for determination of the Ten-day HA values for dimethrin. It is therefore recommended that the Longer-term HA for a 10-kg child (10 mg/L, calculated below) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The 16-week rat study by Masri et al. (1964) has been selected to serve as the basis for determination of the Longer-term HA. In this study, male and female rats were administered dimethrin at dietary levels of 0, 0.2, 0.6, 1.5 or 3.0% for 16 weeks. Results of this study indicated a statistically significant reduction in body weights of males receiving 0.6 or 3.0%, and in females receiving 1.5 or 3.0%. Absolute liver weight and liver-to-body weight ratios were significantly higher in the 1.5- and 3.0%-dose groups. Kidney-to-body weight ratios were also significantly higher in those groups. Histopathological examinations revealed dose-related morphological changes in the liver occurring at dose levels as low as 0.6%. A NOAEL of 0.2% dimethrin (120 mg/kg/day for males; 130 mg/kg/day for females) was identified in this study.

Using a NOAEL of 120 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(120\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 12\ \text{mg/L}\ (10{,}000\ \text{ug/L})$$

where:

120 mg/kg/day = NOAEL, based on absence of hepatic effects in male rats exposed to dimethrin via the diet for 16 weeks.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Using a NOAEL of 120 mg/kg/day, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(120\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 42\ \text{mg/L}\ (40{,}000\ \text{ug/L})$$

where:

120 mg/kg/day = NOAEL, based on absence of hepatic effects in rats exposed to dimethrin via the diet for 16 weeks.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 52-week study in rats by Ambrose (1964) has been selected to serve as the basis for determination of the Lifetime HA for dimethrin. In this study, dimethrin was administered to albino Wistar-CWL rats for 52 weeks at dietary levels of 0, 0.05, 0.1, 0.5, 1.0 or 2.0%. A statistically significant increase in the liver-to-body weight ratio was observed in both male and female rats receiving 1.0 or 2.0% dimethrin (600 and 1,200 mg/kg/day). Histologically, no changes that could be attributed to dimethrin were observed in any of the test groups. No adverse effects were reported in rats receiving dimethrin at 0.5% (300 mg/kg/day for males) or lower.

Using a NOAEL of 300 mg/kg/day, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(300\ \text{mg/kg/day})}{(1{,}000)} = 0.3\ \text{mg/kg/day}$$

where:

300 mg/kg/day = NOAEL, based on absence of increased liver-to-body weight ratio in rats exposed to dimethrin in the diet for 52 weeks.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.3\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 10.5\ \text{mg/L}\ (10{,}000\ \text{ug/L})$$

where:

0.3 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (10.5 mg/L) (20%) = 2.1 mg/L (2,000 ug/L)

where:

10.5 mg/L = DWEL

20% = assumed percentage of daily exposure contributed by ingestion of drinking water.

It should be noted that the Lifetime HA of 2 mg/L apoarently exceeds the water solubility of dimethrin (insoluble).

Evaluation of Carcinogenic Potential

- No information on the carcinogenicity of dimethrin was found in the available literature. However, the report by Cohen and Grasso (1981) implicating dimethrin as a hypolipidemic agent may indicate that dimethrin has carcinogenic potential in rodents. (It should be noted that the relationship between hypolipidemic agents and liver carcinomas in rodents has not been observed in humans.)
- The International Agency for Research on Cancer has not evaluated the carcinogenicity of dimethrin.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), dimethrin may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- No information on existing criteria, guidance, or standards pertaining to dimethrin was found in the available literature. However, tolerances for pyrethroids, of which dimethrin is a member, range from 0.05 ppm in potatoes (post-harvest) to 3 ppm in wheat, barley, rice and oats (CFR, 1985).

VII. ANALYTICAL METHODS

- Dimethrinaisoa cyclopropane carboxviate pesticide which, as such, can be analyzed by EPA Method #616 (U.S. EPA, 1984). This method covers

CHO pesticides such as cycloprate and resmethrin, which are chemically identical to dimethrin. The method is similar to other 600 series methods in that 1 liter of sample is extrcated with methylene chloride and reduced to 1 mL or less. Analysis is by flame-ionization gas chromatography (FID/GC). A cleanup procedure is provided in case interferences are noted.

- While method #616 can be used for monitoring dimethrin, the analyst should demonstrate precision and accuracy data for this compound before proceeding. An estimated detection limit (EDL) should also be determined as specified by regulation (CFR, 1984). The detection limit should fall into the range of 20 to 50 ug/L.

VIII. TREATMENT TECHNOLOGIES

- The manufacture of this compound was discontinued (Meister, 1986). No information was found in the available literature on treatment technologies capable of effectively removing dimethrin from contaminated water.

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August, 1988

DINOSEB

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

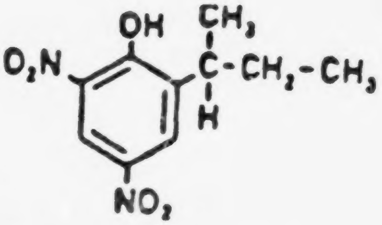
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 88-85-7

Structural Formula



2-sec-butyl-4,6-dinitrophenol

Synonyms

- DNBP, dinitro, dinoseb (BSI, ISO, WSSA); dinosebe (France); Basanite (BASF Wyandotte); Caldon, Chemox General, Chemox PE, Chemsect DNBP, DN-289 (product discontinued), Dinitro, Dinitro-3, Dinitro General, Dynamite (Drexel Chemical); Elgetol 318, Gebutox, Hel-Fire (Helena); Kiloseb, Nitropone C, Premerge 3 (Agway); Sinox General (FMC Corp.); Subitex, Unicrop DNBP, Vertac Dinitro Weed Killer 5, Vertac General Weed Killer, Vertac Selective Weed Killer (Meister, 1984).

Uses

- Dinoseb is used as a herbicide, desiccant and dormant fruit spray (Meister, 1984).

Properties (WSSA, 1983)

Chemical Formula	$C_{10}H_{12}N_2O_5$
Molecular Weight	240
Physical State (room temp.)	Dark amber crystals
Boiling Point	--
Melting Point	32°C
Density (°C)	1.2647 (45°C)
Vapor Pressure	(151°C) 1 mm Hg
Specific Gravity	--
Water Solubility	52 mg/L (25°C)
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Dinoseb has been found in 1 of 89 surface water samples analyzed and in none of 1,270 ground water samples (STORET, 1988). Samples were collected at 89 surface water locations and 1,184 ground water locations, and dinoseb was found in Ohio. The 85th percentile of all nonzero samples was 1 ug/L in surface water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Dinoseb has been found in New York ground water; typical positives were 1 to 5 ppb (Cohen et al., 1986).

Environmental Fate

- Dinoseb was stable to hydrolysis at pH 5, 7, and 9 at 25°C over a period of 30 days (Dzialo, 1984).
- With natural sunlight on a California sandy loam soil, dinoseb had a half-life of 14 hours; with artificial light, it had a half-life of 30 hours, indicating that dinoseb is subject to photolytic degradation (Dinoseb Task Force, 1985a).
- In water with natural sunlight, dinoseb had a half-life of 14 to 18 days; with artificial light, it had a half-life of 42 to 58 days (Dinoseb Task Force, 1985b).
- With soil thin-layer chromatography plates, dinoseb was intermediate to very mobile in silt loam, sand, sandy loam and silty clay loam (Dinoseb Task Force, 1985c).
- Soil adsorption studies gave a K_d of less than 5 for four soils: a silt loam, sand, sandy loam and silty clay loam, with organic matter content of 0.8 to 3% (Dinoseb Task Force, 1985d).

III. PHARMACOKINETICS

Absorption

- Following oral administration of dinoseb to rats (Bandal and Casida, 1972) and mice (Gibson and Rao, 1973) (specific means of administration not specified), approximately 25% of the administered dose appeared in the feces. However, following intraperitoneal (ip) administration in the mouse, approximately 40% appeared in the feces, thus suggesting to Gibson and Rao (1973) that dinoseb is initially completely absorbed following oral administration with subsequent secretion into the gut.

Distribution

- Following oral administration of dinoseb in the mouse (specific means of administration not specified), no appreciable amounts accumulated in the blood, liver or kidney (Gibson and Rao, 1973).

Metabolism

- While the metabolism of dinoseb has not been completely characterized, a number of metabolites have been identified including: 2-(2-butyric acid)-4,6-diaminophenol, 2-(2-butyric acid)-4,6-dinitrophenol, 2-sec-butyl-4-nitro-6-aminophenol, 2-sec-butyl-4-acetamido-6-nitrophenol and 2-(3-butyric acid)-4,6-dinitrophenol (Ernst and Bar, 1964; Froslie and Karlog, 1970; Bandal and Casida, 1972).

Excretion

- In mice, dinoseb is excreted in both urine (20%) and feces (30%) following oral administration (specific means of administration not specified) (Gibson and Rao, 1973).

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- While minimal data are available concerning human toxicity, at least one death has been attributed to an accidental exposure of a farm worker to sprayed dinoseb and dinitro-ortho-cresol (Heyndrickx et al., 1964).

Long-term Exposure

- No information on the long-term health effects of dinoseb in humans was found in the available literature.

Animals

Short-term Exposure

- In rats and mice, the acute oral LD_{50} of dinoseb ranges from 20 to 40 mg/kg (Bough et al., 1965).

Dermal/Ocular Effects

- In rats, the acute dermal toxicity of dinoseb ranges from 67 to 134 mg/kg (Noakes and Sanderson, 1969).
- No other information on the dermal or ocular effects of dinoseb in animals was found in the available literature.

Long-term Exposure

- Hall et al. (1978) reported the results (abstract only) of a feeding study in male and female rats. Eight groups of rats, each group composed of 14 males and 14 females, were exposed to levels of 0, 50, 100, 150, 200, 300, 400 or 500 ppm of dinoseb (80% pure) in the diet for 153 days, respectively. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to 0, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0 and 25.0 mg/kg/day. Mortality was observed at 300 ppm (15 mg/kg/day) and above, and growth was depressed at all dose levels. The LOAEL for this study was identified as 50 ppm (2.5 mg/kg/day), the lowest dose tested.

- In a 6-month dietary study by Spencer et al. (1948), groups of male rats were exposed to dinoseb (99% pure) at levels of 0 (30 animals), 1.35, 2.7, 5.4 (20 animals) and 13.5 mg/kg/day (10 animals). Based on increased mortality at the highest dose and increased liver weight at intermediate doses, the No-Observed-Adverse-Effect Level (NOAEL) for dinoseb was identified as 2.7 mg/kg/day.

- In a study submitted to EPA in support of the registration of dinoseb (Hazleton, 1977), four groups of rats (60/sex/dose) were exposed to dinoseb (purity not specified) in their diets for periods up to two years at dose levels of 0, 1, 3 and 10 mg/kg/day, respectively. Although no evidence of dose-related changes in histopathology, hematology, blood chemistry or certain other parameters were observed, a dose-related decrease in mean thyroid weight was observed in all treated males. The LOAEL in this study was identified as 1 mg/kg/day.

Reproductive Effects

- In a reproduction study by Linder et al. (1982), four groups of ten male rats each were exposed to dinoseb (97% pure) in the diet at levels of 0, 3.8, 9.1 or 15.6 mg/kg/day over an 11-week period, respectively. In addition, a group of five animals was exposed to 22.2 mg/kg/day. The fertility index was reduced to 0 at 22.2 mg/kg and to 10% at 15.6 mg/kg/day; in neither case did the fertility index improve in 104 to 112 days following treatment. A variety of other effects were seen at levels of 9.1 mg/kg/day and higher, including decreased weight of the seminal vesicles, decreased sperm count and an increased incidence of abnormal sperm. The NOAEL for dinoseb in this study was 3.8 mg/kg/day based on a decrease in sperm count and other effects at higher levels.

- In a two-generation rat reproduction study (Irvine, 1981), four groups of rats (25/sex/dose) were exposed to 0, 1, 3, and 10 mg/kg/day of dinoseb in the diet for 29 weeks. Although no reproductive effects were observed in this study per se, a decrease in pup body weight was observed at day 21 post-parturition for all dose levels. Thus, based on a compound-related depression in pup body weight at all dose levels, the LOAEL in this study was 1 mg/kg/day.

Developmental Effects

- Although dinoseb has been reported to be teratogenic (e.g., oligodactyly, imperforate anus, hydrocephalus, etc.) when administered to mice intraperitoneally (Gibson, 1973), it was not teratogenic when administered orally to mice (Gibson, 1973; Gibson and Rao, 1973) or rats (Spencer and Sing, 1982).

- Dinoseb (95% pure), administered to pregnant rats in the diet on days 6 through 15 of gestation, produced a marked reduction in fetal survival at doses of 9.2 mg/kg/day and above but not at doses of 6.9 mg/kg/day (NOAEL) and below (Spencer and Sing, 1982).

- Dinoseb (purity not specified) was without effect in a study in which pregnant mice were orally exposed to a single dose of 15 mg/kg/day (Chernoff and Kavlock, 1983).

- In a developmental toxicity study by Research and Consulting Company (1986), four groups of 16 Chinchilla rabbits were exposed to dinoseb (98% pure) by oral gavage at levels of 0, 1, 3 or 10 mg/kg/day from day 6 to 18 of gestation. At the highest dose level dinoseb produced a statistically significant increase in malformations and/or anomalies when compared to the controls, with external, internal (body cavities and cephalic viscera) and skeletal defects being observed in 11/16 litters examined. Neural tube defects, the major developmental toxic effect, included dyscrania associated with hydrocephaly, scoliosis, kyphosis, malformed or fused caudal and sacral vertebrae and encephalocele. The NOAEL for dinoseb in this study was identified as 3.0 mg/kg/day, based on the occurrence of neural tube defects at the highest dose level.

- In a study by the Dinoseb Task Force (1986), developmental toxicity was observed in Wistar/Han rats. Groups of 25 rats received dinoseb (purity 96.1%) by gavage at levels of 0, 1, 3 or 10 mg/kg/day from day 6 to 15 of gestation. Developmental toxicity was observed at the high dose as evidenced by a slight depression in fetal body weight, increased incidence of absence of skeletal ossification for a number of sites and an increase in the number of supernumerary ribs. Slight to moderate decreases in body weight gain and food consumption were observed in dams at the intermediate- and high-dose levels. Based on the occurrence of developmental effects at the highest dose level, a NOAEL of 3.0 mg/kg/day was identified.

Mutagenicity

- With the exception of an increase in DNA damage in bacteria (Waters, et al., 1982), dinoseb was not mutagenic in a number of organisms including *Salmonella typhimurium*, *Escherichia coli*, *Saccharomyces cerevisiae*, *Drosophila melanogaster* or *Bacillus subtilis* (Simmon et al., 1977; Waters et al., 1982; Moriya et al., 1983).

Carcinogenicity

- No evidence of a carcinogenic response was observed in a 2-year chronic feeding study in which dinoseb was administered to rats at levels as high as 10 mg/kg/day (Hazleton, 1977).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value. It is therefore recommended that the Ten-day HA value for a 10-kg child (0.3 mg/L, calculated below) be used as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The rabbit developmental toxicity study (Research and Consulting Co., 1986) in which dinoseb produced neural tube defects at doses greater than 3 mg/kg/day (NOAEL) was selected as the basis for determination of the Ten-day HA. While it is reasonable to base a Ten-day HA for the adult on a positive developmental toxicity study, there is some question as to whether it is appropriate to base the Ten-day HA for a 10-kg child on a such a study. However, since this study is of appropriate duration and since the fetus may be more sensitive than a 10-kg child, it was judged that, while it may be overly conservative, it is reasonable to base the Ten-day HA for a 10-kg child on such a study.

Using a NOAEL of 3.0 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(3.0 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.3 \text{ mg/L} \quad (300 \text{ ug/L})$$

where:

3.0 mg/kg/day = NOAEL, based on the absence of teratogenic effects in rabbits.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The Hall et al. (1978) 153-day dietary dinoseb study in rats was originally selected to serve as the basis for determination of the Longer-term HA (decreased growth was observed at all exposure levels with a LOAEL of 2.5 mg/kg/day). Subsequently, however, a two-generation reproduction study in rats (Irvine, 1981) was identified with a LOAEL of 1 mg/kg/day (based on a decrease in pup body weight at all dose levels). Since a reproduction study is of appropriate duration, the Irvine (1981) study has been selected to serve as the basis for determination of the Longer-term HA.

Using a LOAEL of 1 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.0 \text{ mg/kg/day})\ (10 \text{ kg})}{(1{,}000)\ (1 \text{ L/day})} = 0.010 \text{ mg/L } (10 \text{ ug/L})$$

where:

1.0 mg/kg/day = LOAEL, based on decreased pup body weight.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.0 \text{ mg/kg/day})\ (70 \text{ kg})}{(1{,}000)\ (2 \text{ L/day})} = 0.035 \text{ mg/L } (40 \text{ ug/L})$$

where:

1.0 mg/kg/day = LOAEL, based on decreased pup body weight.

70 kg = assumed body weight of an adult.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year dietary rat study by Hazelton (1977) was selected to serve as the basis for determination of the Lifetime HA. In this study, a compound-related decrease in mean thyroid weights was observed in all males (LOAEL = 1 mg/kg/day) treated with dinoseb (purity not specified).

Using a LOAEL of 1 mg/kg/day, the Lifetime HA for a 70-kg adult is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(1 \text{ mg/kg/day})}{(1{,}000)} = 0.001 \text{ mg/kg/day}$$

where:

1 mg/kg/day = LOAEL, based on decreased thyroid weight in male rats exposed to dinoseb via the diet for up to 2 years.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.001 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.035 \text{ mg/L } (40 \text{ ug/L})$$

where:

0.001 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.035 mg/L) (20%) = 0.007 mg/L (7 ug/L)

where:

0.035 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenicity was found in a 2-year dietary study in which dinoseb was administered to rats at levels as high as 10 mg/kg/day (Hazleton Labs, 1977).
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of dinoseb.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), dinoseb is classified in Group D: not classified. This group is for agents with inadequate human and animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Tolerances have been established for dinoseb (CFR, 1985) at 0.1 ppm on a wide variety of agricultural commodities.
- The EPA RfD Workgroup approved a 0.001 mg/kg/day RfD for dinoseb. The EPA RfD Workgroup is an EPA wide group whose function is to ensure that consistent RfD values are used throughout the EPA.

VII. ANALYTICAL METHODS

- Analysis of dinoseb is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated acid pesticides in water samples (U.S. EPA, 1985). In this method, approximately 1 liter of sample is acidified. The compounds are extracted with ethyl ether using a separatory funnel. The derivatives are hydrolyzed with potassium hydroxide, and extraneous organic material is removed by a solvent wash. After acidification, the acids are extracted and converted to their methyl esters using diazomethane as the derivatizing agent. Excess reagent is removed, and the esters are determined by electron capture GC. The method detection limit has been estimated at 0.07 ug/L for dinoseb.

VIII. TREATMENT TECHNOLOGIES

- The treatment technologies which will remove dinoseb from water include activated carbon and ion exchange. No data were found for the removal of dinoseb from drinking water by conventional treatment or by aeration. However, limited data suggest that aeration would not be effective in the removal of dinoseb from drinking water (ESE, 1984).

- Becker and Wilson (1978) reported on the treatment of a contaminated lake water with three activated carbon columns operated in series. The columns processed about 2 million gallons of lake water and achieved a 99.98 percent removal of dinoseb. Weber and Gould (1966) performed successful isotherm tests using Columbia LC carbon, which is coconut based, and reported the following Langmuirian equilibrium constants:

  Q = 444 mg dinoseb per g of carbon

  $1/b$ = 1.39 mg/L

  Though the Langmuir equation provides a good fit over a broad concentration range, greater adsorption would probably be achieved at lower concentrations (less than 100 ug/L) than predicted by using these constants.

- Weber (1972) has classified dinoseb as an acidic pesticide; and such compounds have been readily adsorbed in large amounts by ion exchange resins. Harris and Warren (1964) studied the adsorption of dinoseb from aqueous solution by anion exchanger (Amberlite® IRA-400) and a cation exchanger (Amberlite® IR-200). The anion exchanger adsorbed dinoseb to less than detectable limits in solution.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

DIPHENAMID

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

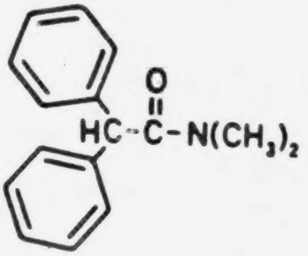
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 957-51-7

Structural Formula



N,N-dimethyl-alpha-phenyl-benzeneacetamide

Synonyms

- ° Dymid; Enide (Meister, 1983).

Uses

- ° Pre-emergent and selective herbicide for tomatoes, peanuts, alfalfa, soybean, cotton and other crops (Meister, 1986).

Properties (Windholz et al., 1983)

Chemical Formula	$C_{16}H_{17}ON$
Molecular Weight	239.30
Physical State (at 25°C)	White crystalline solid
Boiling Point	--
Melting Point	135°C
Density	--
Vapor Pressure (25°C)	--
Specific Gravity	--
Water Solubility (27°C)	260 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- ° Diphenamid has not been found in the 3 surface water samples collected at 2 locations or in 678 groundwater samples taken at 676 locations (STORET, 1988).

Environmental Fate

- ° Diphenamid is stable to hydrolysis at pH 5, 7 and 9 for 7, 12 and 10 days, respectively, at elevated temperature (49°C or 120°F)

(NOR-AM, 1986).

- Diphenamid is intermediately mobile (class 3) on silt loam and silty clay loam soil TLC plates; on sandy loam, it is in class 5, indicating that it would leach readily in this soil (Helling and Turner, 1968).

III. PHARMACOKINETICS

Absorption

- McMahon and Sullivan, (1965) administered 50 mg/kg diphenamid-carbonyl ^{14}C to rats by 3 different routes: oral, intraperitoneal (ip) or subcutaneous (sc) injection. Diphenamid was well absorbed by each of the three routes with peak blood levels being greatest for ip, followed by sc and oral. The half lives of diphenamid in blood for each of the three routes were comparable.

Distribution

- No information was found in the available literature on the distribution of diphenamid.

Metabolism

- In the McMahon and Sullivan (1965) study described above, the main route metabolism of diphenamid was reported as N-dealkylation to nondiphenamid. The nondiphenamid is excreated as the N-glucuranide. p-Hytroxylation was reported as a minor rate of metabolism.

Excretion

- No specific information of the excretion of diphenamid was found in the available literature. However, in the above study, the authors evaluated the urinary metabolites of diphenamid and reported that diphenamid was readily absorbed and metabolized into excretable metabolites.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of diphenamid in humans.

Animals

Short-term Exposure

- RTECS (1987) (attached) reported the acute oral LD_{50} values in the rat, mouse, dog, monkey and rabbit to be 685, 600, 1,000, 1,000 and 1,500 mg/kg, respectively.

Dermal/Ocular Effects

- Weddon and Brown (1976) applied Enide 90W (a 93% wettable powder formulation of diphenamid) to the intact or abraded skin of New Zealand rabbits (two/sex/dose) for 24 hours at 0, 200, 1,000 or 2,000 mg/kg. Neither skin irritation nor systemic effects were observed in any of the exposed animals.

Long-term Exposure

- Woodard et al. (1966b) administered technical diphenamid (purity not specified) in the feed to beagle dogs (three/sex/dose) at dose levels of 0, 3, 10 or 30 mg/kg/day for 103 weeks. No pathological effects were reported at 3 mg/kg/day for clinical chemistry, hematology, urinalysis, gross pathology and histopathology. Liver weights were slightly increased in the 10- and 30-mg/kg/day dosage groups of both sexes, and there were slight increases in numbers of portal macrophages and/or fibroblasts when compared to untreated controls. Liver enzyme levels were normal in all treated groups, except for elevation of serum glutamic-oxaloacetic transaminase (SGOT) after 8 weeks in one female dosed with 3 mg/kg/day. A No-Observed-Adverse-Effect Level (NOAEL) of 3 mg/kg/day and a Lowest-Observed-Adverse-Effect Level (LOAEL) of 10 mg/kg/day were identified by this study.

- Hollingsworth et al. (1966) fed technical diphenamid (>98% pure) to Charles River rats (30/sex/dose) at dose levels of 0, 3, 10 or 30 mg/kg/day for 101 weeks. A slight increase in the mean absolute liver weights of males and the relative liver and thyroid weights of females in the high-dose groups was observed. No other adverse effects were reported at 10 mg/kg/day or less in general behavior, feed consumption, body and organ weights, hematology, gross pathology and histopathology. A NOAEL of 10 mg/kg/day and a LOAEL of 30 mg/kg/day are identified by this study.

Reproductive Effects

- In a three-generation reproduction study, Woodard et al. (1966a) administered technical diphenamid to Charles River albino rats (10 males and 20 females/dose) at dose levels of 0, 10 or 30 mg/kg/day. No reproductive or pathological effects were observed for the parental generations (F_0, F_{1b}, F_{2b}) at any dose tested. Weanlings of the F_{3b} generation dosed with 30 mg/kg/day showed reversible liver changes, including slight congestion, glycogen depletion and irregular size of the hepatocytes. Based on reproductive end points, this study identifies a NOAEL of 30 mg/kg/day. Based on fetal toxicity, a NOAEL of 10 mg/kg/day and a LOAEL of 30 mg/kg/day are identified.

Developmental Effects

- Woodard et al. (1966a) reported no developmental effects in rat pups at any dose level. Reversible liver changes were observed in weanling pups of the F_{3b} generation dosed with 30 mg/kg/day. A NOAEL based on fetotoxicity of 10 mg/kg/day can be identified.

Mutagenicity

- Moriya et al. (1983) reported that diphenamid (up to 5,000 ug/plate) did not increase reversion frequency in *S. typhimurium* or *E. coli* test systems, either with or without metabolic activation.

- Shirasu et al. (1976) reported that diphenamid (1%) was not mutagenic in a recombination assay utilizing *B. subtilis* or in reversion assays with *E. coli* or *S. typhimurium*.

Carcinogenicity

- In a 2-year feeding study in rats by Hollingsworth et al. (1966), diphenamid was administered to Charles River albino rats (30/sex/dose) at dose levels of 0, 3, 10 or 30 mg/kg/day for 101 weeks. Based on histopathological examination of a variety of tissues and organs, the authors reported that the type and incidence of neoplasms were comparable in treated and control rats.

- In a 2-year feeding study in dogs by Woodard et al. (1966b), diphenamid was administered in the feed to beagle dogs (three/sex/dose) at dosage levels of 0, 3, 10 or 30 mg/kg/day for 103 weeks. Histopathological examinations were performed on a variety of tissues and organs, and no evidence of increased tumor frequency was reported.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for diphenamid. It is therefore recommended that the Drinking Water Equivalent Level (DWEL), adjusted for a 10-kg child (0.3 mg/L, calculated below), be used at this time as a conservative estimate of the One-day HA value.

For a 10-kg child, the adjusted DWEL is calculated as follows:

$$\text{DWEL} = \frac{(0.03 \text{ mg/kg/day})\ (10 \text{ kg})}{(1 \text{ L/day})} = 0.3 \text{ mg/L}$$

where:

0.03 mg/kg/day = RfD (see Lifetime Health Advisory Section).

10 kg = assumed body weight of a child.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

No information was found in the available literature that was suitable for determination of the Ten-day HA value for diphenamid. It is therefore recommended that the DWEL, adjusted for a 10-kg child (0.3 mg/L) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

No information was found in the available literature that was suitable for determination of the Longer-term HA value for diphenamid. It is therefore recommended that the DWEL value, adjusted for a 10-kg child (0.3 mg/L) be used at this time as a conservative estimate of the Longer-term HA value.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The feeding study in dogs by Woodard et al. (1966b) has been selected to serve as the basis for determination of the Lifetime HA value for diphenamid. In this study, dogs were administered technical diphenamid (0, 3, 10 or 30 mg/kg/day) in the diet for 103 weeks. Based on clinical chemistry, hematology, urinalysis, gross pathology and histopathology, this study identified a NOAEL of 3 mg/kg/day and a LOAEL of 10 mg/kg/day. The study by Hollingsworth et al. (1966), which identified a NOAEL of 10 mg/kg/day in a 101-week experiment in rats, was not selected, since the rat appears to be somewhat less sensitive than the dog (the NOAEL in the rat is the same as the LOAEL in the dog).

Using a NOAEL of 3 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(3 \text{ mg/kg/day})}{(100)} = 0.03 \text{ mg/kg/day}$$

where:

3 mg/kg/day = NOAEL, based on absence of organ weight loss, clinical chemistry, hematology, urinalysis, gross pathology and histopathology in dogs exposed to diphenamid via the diet for 103 weeks.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.03 \text{ mg/kg/day}) \ (70 \text{ kg})}{(2 \text{ L/day})} = 1.0 \text{ mg/L } (1{,}000 \text{ ug/L})$$

where:

0.03 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (1.0 \text{ mg/L}) \ (20\%) = 0.2 \text{ mg/L } (200 \text{ ug/L})$$

where:

1.0 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- ° No evidence of carcinogenic potential was detected in rats (30/sex/dose) fed diphenamid in the diet for 2 years at a dose level of 30 mg/kg/day (Hollingsworth et al., 1966), or in dogs (three/sex/dose) fed diphenamid in the diet for 2 years, also at a dose of 30 mg/kg/day (Woodward et al., 1966b). These studies are limited by the low doses and the small number of animals employed.
- ° The International Agency for Research on Cancer has not evaluated the carcinogenic potential of diphenamid.
- ° Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), diphenamid is classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- ° Tolerances in or on raw agricultural commodities of 0.01 ppm for milk to 2 ppm for peanut hay and forage have been set for diphenamid (U.S. EPA, 1985).

VII. ANALYTICAL METHODS

- ° Analysis of diphenamid is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. The method detection limit has not been determined for diphenamid but it is estimated that the detection limits for analytes included in this method are in the range of 0.1 to 2 ug/L. This method has been validated in a single laboratory, and the estimated detection limit for the analytes, including diphenamid, is 0.6 ug/L.

VIII. TREATMENT TECHNOLOGIES

- ° Available data indicate that granular activated carbon (GAC) adsorption will remove diphenamid from water.
- ° Whittaker (1980) experimentally determined adsorption isotherms for diphenamid on GAC.
- ° Whittaker (1980) reported the results of GAC columns operating under bench-scale conditions. At a flow rate of 0.8 gpm/sq ft and an empty bed contact time of 6 minutes, diphenamid breakthrough (when effluent

concentration equals 10% of influent concentration) occurred after 500 bed volumes (BV). When two bi-solute diphenamid solutions were passed over the same column, diphenamid breakthrough occurred after 235 BV for diphenamid-propham solution and after 290 BV for diphenamid-fluometuron solution.

° GAC adsorption appears to be the most effective treatment technique for the removal of diphenamid from contaminated water. However, selection of individual or combinations of technologies to attempt diphenamid removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

DISULFOTON

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

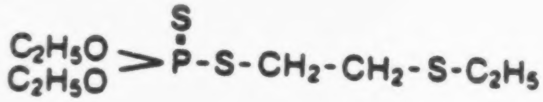
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 298-04-4

Structural Formula



$$\begin{matrix}C_2H_5O\\C_2H_5O\end{matrix}>\overset{S}{\dot{P}}-S-CH_2-CH_2-S-C_2H_5$$

O,O-Diethyl-S-[2-(ethylthio)-ethyl], phosphorodithioate

Synonyms

- Disulfoton; Disyston; Disystox; Dithiodemeton; Bayer 19639; Di-syston; Ethyl thiometon; Frumin AL; M-74 (Meister, 1983).

Uses

- Systemic insecticide-acaricide (Meister, 1983).

Properties (Meister, 1983; Windholz et al., 1983)

Chemical Formula	$C_8H_{19}O_2PS_3$
Molecular Weight	274.38
Physical State (at 25°C)	Pale yellow liquid
Boiling Point	108°C (0.01 mm Hg); 132 to 133°C (1.5 mm Hg)
Melting Point	--
Density (20°C)	1.144
Vapor Pressure (at 20°C)	1.8×10^{-4} mm Hg
Water Solubility (at 23°C)	25 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Disulfoton has been found in only 1 of 368 surface water samples and none of 1,182 ground water samples analyzed (STORET, 1988). The concentration of this surface water sample was 0.34 ug/L. Samples were collected at 93 surface water locations and 1,080 ground water locations. This was also the maximum concentration detected. Disulfoton was detected only in California. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Disulfoton has a low mobility in Hugo sandy loam soil; 28% of the pesticide applied to a 6-inch-high soil column was eluted with a total of 110 feet of dilute buffer (McCarty and King, 1966). In another study, disulfoton sulfoxide and disulfoton sulfone were more mobile in sandy loam, clay loam and silty clay loam soils than the parent compound. Aging ^{32}P-disulfoton prior to elution increased the adsorption to 10 to 20 times that of unaged ^{32}P-disulfoton, meaning that the degradates are probably less mobile than the parent compound. Mobility of disulfoton in soil appears to decrease as organic matter content and cation exchange capacity (EC) increase (Kawamori et al., 1971a, 1971b).

- Insecticidal disulfoton residues are mobile in a silt loam soil as determined by a mosquito bioassay (Lichtenstein et al., 1966). Based on soil thin-layer chromatography (TLC) plates, disulfoton has low mobility in sand (R_f 0.18), sandy loam (R_f 0.16) and silt loam (R_f 0.11 and 0.33), and intermediate mobility in a sandy clay loam soil (R_f 0.39) (Thornton et al., 1976).

- When applied to subirrigated soil columns at 20 lb active ingredient (a.i.) per acre, disulfoton exhibited slight upward mobility in a Hagerstown silty clay loam and a Lakeland sandy loam soil (Mobay Chemical Corporation, 1972). Disulfoton (6 lb/gal EC), applied at 4 lb ai/A to sloping field plots (1 inch/ft) of sandy loam, silt loam and highly organic silt loam soils, was slightly mobile in runoff water. Disulfoton concentrations measured about 1.6% of applied amounts over a 28-day period in which 1.5 to 2.5 inches of irrigation was applied (Flint et al., 1970).

- Disulfoton (granular, G) dissipates rapidly in field plots of sandy loam soil treated at 2 kg/ha (incorporated to a depth of 10 cm), with a half-life of 1 week, and 90% loss after 5 weeks. Disulfoton sulfoxide has a half-life of 8 to 10 weeks, while disulfoton sulfone remains fairly stable over a 42-week period. Disulfoton sulfone was detected at a depth of 20 cm (Suett, 1975). Disulfoton residues dissipated with half-lives of 1 to 6 months in muck-sand, silt loam, and clay soils treated with disulfoton 10% G or 6 lb/gal EC at 10 ppm. Dissipation from the upper 6 inches was enhanced by increasing amounts of rainfall (Chemagro Corporation, 1969; Loeffler, 1969; Mobay Chemical Corporation 1964).

- Disulfoton is likely to be found in runoff water and sediment from treated and cultivated fields. In monitoring studies conducted in 1973 and 1974, disulfoton was found at average concentrations of

13.8 ppb in sediment samples taken from tailwater pits receiving irrigation and rainfall runoff water from cultivated silt loam corn fields. The maximum concentration in sediment samples was 32.7 ppb. The compound was also detected in soil samples from a tailwater pit draining silt loam corn and sorghum fields at an average concentration of 11 ppb. Sediment samples in tailwater pits draining sorghum fields contained disulfoton at a concentration of 117.2 ppb (Kadoum and Mock, 1978).

III. PHARMACOKINETICS

Absorption

- Puhl and Fredrickson (1975) administered by gavage single oral doses of disulfoton-o-ethyl-1-^{14}C (99% purity) to Sprague-Dawley rats (12/sex/dose). Males received 1.2 mg/kg and females received 0.2 mg/kg. In the 10 days following dosing, an average of 81.6, 7.0 and 9.2% of the dose was recovered in the urine, feces and expired air, respectively. Males excreted 50% of the administered dose in the urine in the first 4 to 6 hours; females required 30 to 32 hours. These data indicate that disulfoton is absorbed readily from the gastrointestinal tract.

Distribution

- In the study by Puhl and Fredrickson (1975), described above, 4.1 and 16.1% of the administered dose was detected in the livers of males and females, respectively, and 0.4 and 1.2% of the dose was detected in the kidneys of males and females, respectively, 48 hours postdosing.

Metabolism

- March et al. (1957) studied the metabolism of disulfoton *in vivo* and *in vitro* in mice (strain not specified). In the *in vivo* portion of the study, mice received radiolabeled disulfoton intraperitoneally (dose not specified). Results indicated that unspecified urinary metabolites consisted mainly of hydrolysis products. *In vitro* metabolism data indicated the presence of dithio-systox sulfoxide and sulfone, and the thiol analog sulfoxide and sulfone. The dithio-systox sulfoxide was present in the greatest quantity followed by thiol analog sulfoxide, dithio-systox sulfone and thiol analog sulfone. Based on a review of these data (U.S. EPA, 1984a), it was concluded that the metabolism of disulfoton in mice involves at least two reactions: (1) the sequential oxidation of the thioether sulfur and/or oxidative desulfuration; and (2) hydrolytic cleavage of the ester, producing phosphoric acid, thiophosphoric acid and dithiophosphoric acid.

- In the above study by Puhl and Fredrickson (1975), the major urinary metabolites detected in both sexes were diethylphosphate (DEP) and diethylphosphorothioate (DEPT). These products were formed from hydrolysis of disulfoton and/or its oxidation products. Minor urinary metabolites included the oxygen analog sulfoxide, oxygen analog sulfone and disulfoton sulfoxide.

Excretion

- In the above study by Puhl and Fredrickson (1975), 97.8% of the administered dose was recovered (81.6% in urine, 7.0% in feces and 9.2% as expired carbon dioxide during a 10-day postdosing period. Excretory pathways were similar for males and females, but the rate of excretion was slower for females.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- No significant anticholinesterase effects were observed in human subjects (five test subjects, two controls) who received disulfoton in doses of 0.75 mg/day (orally) for 30 days (Rider et al., 1972).
- Quinby (1977) reported that three carpenters were sprayed accidentally with disulfoton while the compound was being applied by airplane to a wheat field adjacent to their work site. The individuals were reexposed as they handled contaminated building materials in the days following spraying. Exposure levels were not identified. The older two carpenters experienced coronary attacks and one had at least two severe cerebral vascular effects subsequent to exposure. The author postulated that the effects may have been due to disturbances of clotting mechanisms.

Long-term Exposure

- No Long-term human studies were identified for disulfoton.

Animals

Short-term Exposure

- Reported acute oral LD_{50} values for adult rats administered disulfoton (approximately 94 to 96% purity when identified) ranged from 1.9 to 2.6 mg/kg for females and 6.2 to 12.5 mg/kg for males (Crawford and Anderson, 1974; Bombinski and DuBois, 1957); a value of 5.4 mg/kg was reported for weanling male rats (Brodeur and Dubois, 1963).
- In guinea pigs, acute oral LD_{50} values ranged from 8.9 to 12.7 mg/kg (Bombinski and Dubois, 1957; Crawford and Anderson, 1973).
- Mihail (1978) reported acute oral LD_{50} values of 7.0 mg/kg and 8.2 mg/kg in male and female NMRI mice, respectively.

- Hixson (1982) reported that the acute oral LD_{50} of disulfoton (97.8% pure) in white Leghorn hens was 27.5 mg/kg. Hixson (1983) reported the results of an acute delayed neurotoxicity study in which 20 white Leghorn hens were administered technical disulfoton (97.8% pure) by gavage at a dose level of 30 mg/kg on two occasions, 22 days apart. The study also employed groups of 5, 10 and 5 hens for positive controls, antidote controls and negative controls, respectively. Disulfoton did not produce acute delayed neurotoxicity under the conditions of this study. Based on this information, a No-Observed-Adverse-Effect Level (NOAEL) of 30 mg/kg (the only dose tested) was identified in this study.

- Taylor (1965) reported the results of a demyelination study in which white Leghorn hens (six/dose) were administered disulfoton in the diet for 30 days at concentrations of 0, 2, 10 or 25 ppm, these dietary levels are equivalent to 0, 0.1, 0.6 and 1.5 mg/kg/day. The author indicated that no evidence of demyelination was observed in any of the tissues examined. Based on this information, a NOAEL of 1.5 mg/kg/day (the highest dose tested) was identified.

Dermal/Ocular Effects

- DuBois (1957) reported that the acute dermal LD_{50} of technical disulfoton in male Sprague-Dawley rats was 20 mg/kg. Mihail (1976) reported acute dermal LD_{50} values of 15.9 mg/kg and 3.6 mg/kg in male and female Wistar rats, respectively.

- No information was found in the available literature on the effects of ocular exposure to disulfoton.

Long-term Exposure

- Hayes (1983) presented the results of a 23-month feeding study in which CD-1 mice (50/sex/dose) were administered disulfoton (98.2% pure) at dietary concentrations of 0, 1, 4 or 16 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these dietary levels correspond to doses of about 0, 0.15, 0.6 and 2.4 mg/kg/day. No treatment-related effects were observed in terms of body weight, food consumption or hematology. A statistically significant increase in mean kidney weight and kidney-to-body weight ratio was noted in high-dose females; this increase may have been associated with a nonsignificant increase in the incidence of malignant lymphomas of kidneys in this group. Plasma, red blood cell and brain cholinesterase (ChE) activity was decreased significantly in both sexes at the highest dose tested (16 ppm). However, since ChE activity was measured only in the control and high-dose groups, a NOAEL for this effect could not be determined.

- In a study by Hoffman et al. (1975), beagle dogs (four/sex/dose) were administered disulfoton (95.7% pure) at dietary concentrations of 0, 0.5 or 1.0 ppm for 2 years. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), these dietary levels correspond to doses of about 0, 0.0125 and 0.025 mg/kg/day. A fourth group of animals received disulfoton in the diet at 2 ppm for 69 weeks, then 5 ppm for weeks 70 to 72, and finally 8 ppm from week 73 until termination (104 weeks); these doses correpond to 0.05, 0.125 and 0.2 mg/kg/day, respectively. No treatment-related effects were observed in terms of general appearance, behavior, ophthalmoscopic examinations, food consumption, body weight, organ weight, hematology, clinical chemistry or histopathology. Additionally, no effects on ChE activity were observed in animals that received 0.5 or 1.0 ppm (0.0125 or 0.025 mg/kg/day). However, exposure at 2.0 ppm (0.05 mg/kg/day) for 69 weeks caused ChE inhibition in plasma and red blood cells in both sexes. Maximum inhibition occurred at week 40, when males exhibited 50% and 33% inhibition of ChE in red blood cells and plasma; respectively; females exhibited 22 and 36% inhibition of ChE in red blood cells and plasma, respectively. At a dose level of 8 ppm (0.2 mg/kg/day), males exhibited 56 to 66% and 63 to 70% inhibition of red blood cell and plasma ChE, respectively; females exhibited 46 to 53% and 54 to 64% inhibition of red blood cell and plasma ChE, respectively. Based on these data, a NOAEL of 1.0 ppm (0.025 mg/kg/day) was identified.

° Carpy et al. (1975) presented the results of a 2-year feeding study in which Sprague-Dawley rats (60/sex/dose) were administered disulfoton (95.7% pure) at dietary concentrations of 0, 0.5, 1.0 or 2.0 ppm. Based on data presented by the authors, these dietary levels correspond to doses of about 0, 0.02, 0.05 and 0.1 mg/kg/day for males and 0, 0.03, 0.04 and 0.1 mg/kg/day for females. At week 81 of the study, the 0.5-ppm dose was increased to 5.0 ppm (0.2 and 0.3 mg/kg/day for males and females, respectively) since no adverse effects were observed in the 1.0-ppm dose group. No treatment-related effects were observed in terms of food consumption, body weight, hematology, clinical chemistry, urinalysis and histopathology. A trend was observed at all dose levels toward increased absolute and relative spleen, liver, kidney and pituitary weights in males and toward decreased weights of these organs in females. In males receiving 5 ppm, the increases were statistically significant ($p < 0.05$) for absolute spleen and liver weights. In females receiving 5 ppm, the decrease in absolute and relative kidney weights was statistically significant ($p < 0.05$). At all levels tested, the brain showed a trend toward decreased absolute and relative weights in males and increased weights in females. Additionally, statistically significant inhibition of plasma, red blood cell and brain ChE was observed in both sexes at 2.0 and 5.0 ppm. At 1.0 ppm brain ChE in females was inhibited 11% ($p < 0.01$). Based on this information, a Lowest-Observed-Adverse-Effect Level (LOAEL) of 1.0 ppm (0.04 mg/kg/day for females) was identified for ChE inhibition. It was concluded (U.S. EPA, 1984a) that a NOAEL for systemic toxicity could not be identified due to the inadequacy of histopathology and necropsy data.

° Hayes (1985) presented the results of a 2-year feeding study in which Fischer 344 rats (60/sex/dose) were administered disulfoton (97.91% pure) at dietary concentrations of 0, 0.8, 3.3 or 13 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these dietary levels correspond to doses of about

0, 0.04, 0.17 and 0.65 mg/kg/day. Mortality was generally low for all groups with the exception of increased mortality in high-dose females during the last week of the study. No compound-related effects were observed in terms of clinical chemistry, hematology or urinalysis. A dose-related trend in ChE inhibition was observed in both sexes at all dose levels. Statistically significant inhibition of plasma, red blood cell and brain ChE occurred in all dose groups throughout the study. Histopathologically, a statistically significant increase ($p < 0.05$) in corneal neovascularization was observed in both sexes at 13 ppm (0.65 mg/kg/day). A dose-related increase in the incidence of optic nerve degeneration was also observed. This effect was statistically significant ($p < 0.05$) in mid-dose males and in mid- and high-dose females. Additionally, a significantly ($p < 0.05$) higher incidence of cystic degeneration of the Harderian gland was observed in females at all doses and in mid-dose males. A significantly ($p < 0.05$) increased incidence of atrophy of the pancreas also was observed in high-dose males. On the basis of ChE inhibition, this study identified a LOAEL of 0.8 ppm (0.04 mg/kg/day) (lowest dose tested).

Reproductive Effects

- Taylor (1966) conducted a three-generation reproduction study in which albino Holtzman rats (20 females and 10 males) were administered disulfoton (99.5% pure) at dietary concentrations of 0, 2, 5 or 10 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these dietary levels correspond to doses of about 0, 0.1, 0.25 and 0.5 mg/kg/day. At 10 ppm (0.5 mg/kg/day), litter size was reduced by 21% in the F_a and 33% in the F_b in both the first and third generations. Also in these generations, a 10 to 25% lower pregnancy rate was noted for F_a matings. Histopathologically, F_{3b} litters at 10 ppm (0.5 mg/kg/day) exhibited cloudy swelling and fatty infiltration of the liver (both sexes), mild nephropathy in kidneys (both sexes) and juvenile hypoplasia of the testes. No histopathological examinations were conducted on the 2- and 5-ppm dose groups. Cholinesterase determinations revealed a 60 to 70% inhibition of red blood cell ChE in F_{3b} litters and their parents at 5 and 10 ppm (0.25 and 0.5 mg/kg/day). At 2 ppm (0.1 mg/kg/day), the inhibition was insignificant in males and moderate (32 to 42%) in females. Based on these data, a LOAEL of 2 ppm (0.1 mg/kg/day) was identified for ChE inhibition. It was concluded (U.S. EPA, 1984a) that a reproductive NOAEL could not be determined due to deficiencies in data reporting (e.g., insufficient data on reproductive parameters, no statistical analyses, incomplete necropsy report and insufficient histopathology data).

Developmental Effects

- Lamb and Hixson (1983) conducted a study in which CD rats (25/dose) were administered disulfoton (98.2% pure) by gavage at levels of 0, 0.1, 0.3 or 1 mg/kg/day on days 6 through 15 of gestation. Mean plasma and red blood cell ChE activities were decreased significantly in dams receiving 0.3 and 1 mg/kg/day. Examination of the fetuses after Cesarean section reflected no increases in the incidence of soft tissue, external or skeletal abnormalities. However, at the 1.0 mg/kg/day dose level, increased incidences of incompletely ossified parietal bones and sternebrae were observed. This is considered a fetotoxic effect, since it is indicative of retarded development. Based on the information presented in this study, a developmental NOAEL of 0.3 mg/kg/day was identified based on fetotoxic effects. A NOAEL of 0.1 mg/kg/day was identified for ChE inhibition in treated dams.

- Tesh et al. (1982) conducted a teratogenicity study in which New Zealand White rabbits were administered disulfoton (97.3% pure) at initial doses of 0, 0.3, 1.0 or 3.0 mg/kg on days 6 through 18 of gestation. Due to mortality and signs of toxicity, the high dose was reduced to 2.0 mg/kg/day and finally to 1.5 mg/kg/day. The control group consisted of 15 animals, the low- and mid-dose groups consisted of 14 does each and the high-dose group contained 22 animals. No signs of maternal toxicity were observed in the low- or mid-dose groups. In the high-dose group, signs of maternal toxicity included muscular tremors, unsteadiness and incoordination, increased respiratory rate and increased mortality. No compound-related effects on maternal body weight or fetal survival, growth and development were observed. Based on this information, a NOAEL of 1.0 mg/kg/day was identified for maternal toxicity. The NOAEL for teratogenic and fetotoxic effects was 1.5 mg/kg/day (the highest dose tested).

Mutagenicity

- Hanna and Dyer (1975) reported that disulfoton (99.3% pure) was mutagenic in Salmonella typhimurium strains C 117, G 46, TA 1530 and TA 1535, and in Escherichia coli strains WP 2, WP 2uvrA, CM 571, CM 611, WP 67 and WP 12. These tests were performed without metabolic activation; however, demeton-S-methyl sulphoxide, the major metabolite of disulfoton, was also mutagenic in these microbial tests (U.S. EPA, 1984a).

- Simmon (1979) presented the results of an unscheduled DNA synthesis assay using human fibroblasts (W I38). Disulfoton (purity not specified) was positive in this assay only in the absence of metabolic activation.

Carcinogenicity

- Carpy et al. (1975) presented the results of a 2-year feeding study in which Sprague-Dawley rats (60/sex/dose) were administered disulfoton (95.7% pure) at dietary concentrations of 0, 0.5, 1.0 or 2.0 ppm. Based on data presented by the authors, these dietary levels correspond to doses of about 0, 0.02, 0.05 and 0.1 mg/kg/day for males and 0, 0.03, 0.04 and 0.1 mg/kg/day for females. At week 81 of the study, the 0.5-ppm dose was increased to 5.0 ppm (reported to be equivalent to 0.2 and 0.3 mg/kg/day for males and females, respectively) since no adverse effects were observed in the 1.0-ppm dose group. The number of tumor-bearing animals at all dose levels was comparable to that of controls suggesting that, under the conditions of this study, disulfoton is not oncogenic. However, a review of this study (U.S. EPA, 1984a) concluded that due to numerous deficiencies (e.g., invalid high dose, insufficient necropsy data, insufficient histology data), the data presented were inadequate for an oncogenic evaluation.

° Hayes (1983) presented the results of a 23-month feeding study in which CD-1 mice (50/sex/dose) were administered disulfoton (98.2% pure) at dietary concentrations of 0, 1, 4 or 16 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these dietary levels correspond to doses of about 0, 0.15, 0.6 and 2.4 mg/kg/day. The incidence of specific neoplasms was similar among treated and control animals. There was an increased incidence of malignant lymphoma (the most frequently observed neoplastic lesion) in both males and females at 16 ppm (2.4 mg/kg/day) when compared with controls, but this change was not statistically significant. Therefore, under the conditions of this study, disulfoton was not oncogenic in mice at dietary concentrations up to 16 ppm (2.4 mg/kg/day).

° Hayes (1985) presented the results of a 2-year feeding study in which Fischer 344 rats (60/sex/dose) were administered disulfoton (97.91% pure) at dietary concentrations of 0, 0.8, 3.3 or 13 ppm, corresponding doses of about 0, 0.04, 0.17 and 0.65 mg/kg/day (Lehman, 1959). The most commonly occurring neoplastic lesions included leukemia, adenoma of the adrenal cortex, pheochromocytoma, fibroadenoma of the mammary glands, adenoma and carcinoma of the pituitary glands, interstitial cell adenoma of the testes, and uterine stromal polyps. The incidences of these lesions showed no dose-related trend and were not significantly different in treated versus control animals. Therefore, under the conditions of this assay, disulfoton was not oncogenic in male or female Fischer 344 rats at dietary concentrations up to 13 ppm (0.65 mg/kg/day).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\underline{\quad}\ \text{L/day})} = \underline{\quad}\ \text{mg/L}\ (\underline{\quad}\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable information was found in the available literature for the determination of a One-day HA value for disulfoton. It is, therefore, recommended that the Ten-day HA value for a 10-kg child of 0.01 mg/L (10 ug/L), calulated below, be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The developmental toxicity study by Lamb and Hixson (1983) has been selected to serve as the basis for the Ten-day HA value for disulfoton. In this study, CD rats were administered disulfoton (98.2% pure) by gavage at doses of 0, 0.1, 0.3 or 1 mg/kg/day on days 6 through 15 of gestation. Mean plasma and red blood cell ChE activities were decreased significantly in dams receiving 0.3 and 1 mg/kg/day. Based on this information, a NOAEL of 0.1 mg/kg/day was identified. The only other study of comparable duration was a rabbit teratology study (Tesh et al., 1982). This study identified NOAELs of 1.0 mg/kg/day for maternal toxicity and 1.5 mg/kg/day (the highest dose tested) for developmental toxicity. The rabbit appeared to be less sensitive to disulfoton than the rat, therefore the rat study was selected for this calculation.

Using a NOAEL of 0.1 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.1 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.01 \text{ mg/L } (10 \text{ ug/L})$$

where:

0.1 mg/kg/day = NOAEL, based on the absence of ChE effects in female rats administered disulfoton by gavage on days 6 through 15 of gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption by a child.

Longer-term Health Advisory

The 2-year dog feeding study by Hoffman et al. (1975) has been selected to serve as the basis for the Longer-term HA values for disulfoton. In this study, beagle dogs were administered disulfoton (95.7% pure) at dietary concentrations of 0, 0.5 or 1.0 ppm (0, 0.0125 and 0.025 mg/kg/day). A fourth group of dogs received disulfoton at 2.0 ppm (0.05 mg/kg/day) for

69 weeks, then 5.0 ppm (0.125 mg/kg/day) for weeks 70 to 72, and finally 8.0 ppm (0.2 mg/kg/day) from weeks 73 to 104. Exposure to 2.0 ppm (0.05 mg/kg/day) for 69 weeks caused plasma and red blood cell ChE inhibition in both sexes. Brain ChE inhibition was also noted at termination in this group. Based on this information, a NOAEL of 1.0 ppm (0.025 mg/kg/day) was identified. No other suitable studies were available for consideration for the Longer-term HA. Since the effects in the study by Hoffman et al. (1975) were observed following 69 weeks of exposure, the study is considered to be of appropriate duration for derivation of a Longer-term HA.

Using a NOAEL of 0.025 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.025\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.0025\ \text{mg/L}\ (3\ \text{ug/L})$$

where:

0.025 mg/kg/day = NOAEL, based on the absence of ChE effects in dogs administered disulfoton in the diet; ChE effects were noted at the higher dose during the first 40 to 69 weeks of exposure and thereafter.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Using a NOAEL of 0.025 mg/kg/days, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.025\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 0.0088\ \text{mg/L}\ (9\ \text{ug/L})$$

where:

0.025 mg/kg/day = NOAEL, based on the absence of ChE effects in dogs administered disulfoton in the diet; ChE effects were noted at the higher dose during the first 40 to 69 weeks of exposure and thereafter.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor. From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The studies by Hayes (1985) and Carpy et al. (1975) have been selected to serve as the bases for the Lifetime HA values for disulfoton. Each of these studies identifies a LOAEL of 0.04 mg/kg/day. In the Hayes (1985) study, Fischer 344 rats were administered disulfoton (98.1% pure) at dietary concentrations of 0, 0.8, 3.3 or 13 ppm (0, 0.04, 0.17 and 0.65 mg/kg/day) for 2 years. Dose-related, statistically significant inhibition of ChE in plasma, red blood cell and brain was observed in both sexes at all doses; also, a dose-related optic nerve degeneration was observed in females. Based on this information, a LOAEL of 0.04 mg/kg/day was identified. In the Carpy et al. (1975) 2-year study, Sprague-Dawley rats were administered disulfoton (95.7% pure) at dietary concentrations of 0, 0.5, 1.0 or 2.0 ppm (0, 0.02, 0.05 and 0.1 mg/kg/day for males and 0, 0.03, 0.04 and 0.1 mg/kg/day for females). At week 81 of the study, the 0.5 ppm dose was increased to 5.0 ppm (equivalent to 0.2 and 0.3 mg/kg/day for males and females, respectively). Statistically significant inhibition of plasma and red blood cell ChE was observed in both sexes at 2.0 and 5.0 ppm. Additionally, at 1 ppm (0.04 mg/kg/day), brain ChE was inhibited significantly ($p < 0.01$) in females. Since the initial low dose used in the study (0.5 ppm) was raised to 5.0 ppm, the 1.0-ppm dose is the lowest dose tested and represents the study LOAEL.

Using a LOAEL of 0.04 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.04\ \text{mg/kg/day})}{(1{,}000)} = 0.00004\ \text{mg/kg/day}$$

where:

0.04 mg/kg/day = LOAEL, based on ChE inhibition and optic nerve degeneration in rats exposed to disulfoton in the diet for 2 years.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.00004\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.0014\ \text{mg/L}\ (1\ \text{ug/L})$$

where:

0.00004 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory (HA)

$$\text{Lifetime HA} = (0.0014\ \text{mg/L})(20\%) = 0.0003\ \text{mg/L}\ (0.3\ \text{ug/L})$$

where:

0.0014 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Three studies were available on the carcinogenicity of disulfoton. The chronic study in rats by Carpy et al. (1975) was inadequate for an oncogenic evaluation. The remaining two studies presented results indicating that disulfoton was not carcinogenic in mice (Hayes, 1983) or in rats (Hayes, 1985).

- The International Agency for Research on Cancer has not evaluated the carcinogenicity of disulfoton.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), disulfoton may be classified in Group E: no evidence of carcinogenicity in humans. This category is used for substances that show no evidence of carcinogenicity in at least two adequate animal tests or in both epidemiologic and animal studies. However, disulfoton and its metabolites are mutagenic compounds (see section on Mutagenicity).

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

° The National Academy of Sciences (NAS, 1977) has calculated an ADI of 0.0001 mg/kg/day, based on a NOAEL of 0.01 mg/kg/day from a subchronic dog feeding study on phorate (a closely related organophosphorus insecticide) and an uncertainty factor of 100, with a Suggested-No-Adverse-Response-Level (SNARL) of 0.0007 mg/L.

° The World Health Organization (WHO, 1976) has identified an ADI of 0.002 mg/kg/day based on chronic data from a 2-year chronic feeding study in dogs (Hoffman et al., 1975) with a NOAEL of 0.025 mg/kg/day.

° U.S. EPA Office of Pesticide Programs (OPP) has established residue tolerances for disulfoton at 0.1 to 0.75 ppm in or on a variety of raw agricultural commodities (U.S. EPA, 1985). At the present time, these tolerances are based on a Provisional ADI (PADI) of 0.00004 mg/kg/day. As for the RfD calculation, this PADI is calculated based on a LOAEL of 0.8 ppm (0.04 mg/kg/day) for both ChE inhibition and optic nerve degeneration that were identified in the 2-year rat feeding study by Hayes (1985) and using a safety factor of 1,000.

VII. ANALYTICAL METHODS

° Analysis of disulfoton is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus-containing pesticides in water samples (Method #507, U.S. EPA, 1988). In this method, approximately 1 L of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen-phosphorus detector. The method has been validated in a single laboratory and the estimated detection limit for the analytes in this method, including disulfoton, is 0.3 ug/L.

VIII. TREATMENT TECHNOLOGIES

° No information was found in the available literature regarding treatment technologies used to remove disulfoton from contaminated water.

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*Confidential Business Information submitted to the Office of Pesticide Programs

August, 1988

DIURON

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

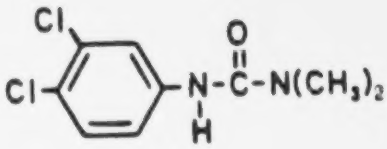
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 330-54-1

Structural Formula



N'-(3,4-Dichlorophenyl)-N,N-dimethylurea

Synonyms

- Cekiuron, Crisuron, Dailon, Diater, Di-on, Direx 4L, Ditox-800, Diurex, Diurol, Drexel Diuron 4L, Dynex, Farmco Diuron, Karmex, Unidron, Vonduron. Discontinued names: Sup'r Flo, Urox 'D' (Meister, 1988).

Uses

- Herbicide. Diuron at low rates as a selective herbicide to control germinating broadleaf, grass weeds in numerous crops such as sugarcane, pineapple, caneberries, alfalfa, grapes, cotton, and peppermint. General weed killer at higher rates. As soil sterilant, more persistent and preferred over monuron on lighter soil and/or in areas of heavy rainfall. Drexel Diuron 4L, Farmco Diuron Flowable control weeds in wheat, barley, citrus, vineyards, bananas, pineapple, cotton, and noncrop areas (Meister, 1988).

Properties (Meister, 1988; Windholz et al., 1983)

Chemical Formula	$C_9H_{10}N_2OCl_2$
Molecular Weight	233.10
Physical State (at 25°C)	White crystalline solid
Boiling Point	--
Melting Point	158-159°C
Density	--
Vapor Pressure (50°C)	3.1 x 10^{-6} mm Hg
Specific Gravity	--
Water Solubility (25°C)	42 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Diuron has been found in none of the 25 surface water samples analyzed and in none of 1,337 ground water samples (STORET, 1988). Samples were collected at 22 surface water locations and 1,292 ground water locations.

- Diuron residues as a result of agricultural practice have been detected in ground waters in California in wells at low (e.g., 2 to 3 ppb) levels (California Department of Food and Agriculture, 1986).

Environmental Fate

- Radiolabeled diuron and its degradation products 3-(3,4-dichlorophenyl)-1-methylurea (DCPMU) and 3-(3,4-dichlorophenyl)urea (DCPU) had half-lives of 4 to 8, 5, and 1 month, respectively, in aerobic soils maintained at 18 to 29°C and moisture levels at approximately field capacity (Walker and Roberts, 1978; Elder, 1978). 3,4-Dichloroaniline (DCA) was identified as a minor degradation product of diuron (Belasco, 1967; Belasco and Pease, 1969; Elder, 1978). Increasing soil organic matter content appears to increase the rate of decline of diuron phytotoxic residues (McCormick, 1965; Corbin and Upchurch, 1967; McCormick and Hiltbold, 1966; Liu et al., 1970).

- Degradation of diuron phytotoxic residues is much (28 to 50%) slower in flooded soil than in aerobic soil (Imamliev and Bersonova, 1969; Wang et al., 1977).

- Diuron has a low-to-intermediate mobility in fine to coarse-textured soils and freshwater sediments (Hance 1965a,b; Harris and Sheets, 1965; Harris, 1967; Helling and Turner, 1968; Grover and Hance, 1969; Gerber et al., 1971; Green and Corey, 1971; Helling, 1971; Guth, 1972; Grover, 1975; Helling, 1975). Mobility is correlated with organic matter content and cation exchange capacity (CEC). Soil texture apparently is not, by itself, a major factor governing the mobility of diuron in soil.

- In a study using radiolabeled material, the diuron degradation products (96% pure) had K_d values of 66 and 115 in silty clay loam soils, indicating that they are relatively immobile or less mobile than diuron (Elder, 1978).

- In the field, diuron residues (nonspecific method used) generally persisted for up to 12 months in soils that ranged in texture from sand to silt loam treated with diuron at 0.8 to 4 lb/A (Cowart, 1954; Hill et al., 1955; Weed et al., 1953; Weed et al., 1954; Miller et al., 1978). These residues may leach in soil to a depth of 120 cm (4 feet). Diuron was detectable (3 to 74 ppb) in runoff-water sediment and soil samples for up to 3 years after the last application to pineapple-sugarcane fields in Hawaii (Mukhtar, 1976; Green et al., 1977). Diuron may have the potential to leach into ground water.

- Phytotoxic residues persisted for up to 12 months in soils ranging in texture from sand to silty clay loam to boggy meadow soil following the last of one to six annual applications of diuron at 1 to 18 lb/A (Weldon and Timmons, 1961; Dalton et al., 1965; Bowmer, 1972; Dawson et al., 1978; Arle et al., 1965; Wang and Tsay, 1974; Spiridonov et al., 1972; Addison and Bardsley, 1968; Cowart, 1954; Hill et al., 1955; Weed et al, 1953; Weed et al., 1954). Diuron persistence in soil appears to be a function of application rate and amount of rainfall and/or irrigation water. Three degradation products (DCPMU, DCPU, and DCA) were identified in soil (planted with cotton) that had received multiple applications of diuron (80% wettable powder totaling 5 to 5.7 lb/A (Dalton et al., 1965).

° Diuron persists in irrigation-canal soils for 6 or more months following application at 33 to 46 kg/ha (Evans and Duseja, 1973a; Evans and Duseja, 1973b; Bowmer and Adeney, 1978a; Bowmer and Adeney, 1978b). The relative percentages of diuron and its degradates DCPMU and DCPU were 60-90:10-25:1-30 in clay and sandy clay soils, 4.5 to 17 weeks after treatment. Diuron levels in water samples were highest (0.5 to 8 ppm) in the initial flush of irrigation water. These levels declined rapidly, probably as a function of dilution and not degradation.

III. PHARMACOKINETICS

Absorption

° Diuron is absorbed through the gastrointestinal tract of rats and dogs. Hodge et al. (1967) fed diuron to rats and dogs at dietary levels from 25 to 2,500 ppm and from 25 to 1,250 ppm active ingredient (a.i.), respectively, for periods up to two years. These doses are equivalent to 1.25 to 125 mg/kg/day for the rat and 0.625 to 31.25 mg/kg/day for the dog. Urinary and fecal excretion products after one week to 2 years accounted for about 10% of the daily dose ingested. The excretion data provided evidence that gastrointestinal absorption ocurred in rats and dogs.

Distribution

° Hodge et al. (1967) fed diuron (80% wettable powder) for 2 years to rats at dietary levels of 25 to 2,500 ppm a.i. and to dogs at dietary levels of 25 to 1,250 ppm a.i. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day in rats and 0.025 mg/kg/day in dogs, this corresponds to doses of 1.25 to 125 mg/kg/day in rats and 0.625 to 31.25 mg/kg/day in dogs (Lehman, 1959). Analysis of tissue samples for diuron residues revealed levels ranging from 0.2 to 56 ppm, depending on dose. This constituted only a minute fraction of the total dose ingested. The authors concluded that there was little diuron storage in tissues.

Metabolism

° Geldmacher von Mallinckrodt and Schlussier (1971) analyzed the urine of a woman who had ingested a dose of 38 mg/kg of diuron along with 20 mg/kg of aminotriazole. The urine was found to contain 1-(3,4-dichlorophenyl)-3-methylurea and 1-(3,4-dichlorophenyl)-urea, and may also have contained some 3,4-dichloroaniline. No unaltered diuron was detected.

- Hodge et al. (1967) fed diuron (80% wettable powder) to male beagle dogs at a dietary level of 125 ppm active ingredient for 2 years. Assuming that 1 ppm in the diet is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to a dose of 3.1 mg/kg/day. Analysis of urine at weeks one to four or after two years revealed the major metabolite was N-(3,4-dichlorophenyl)-urea. Small amounts of N-(3,4-dichlorophenyl)-N'-methylurea, 3,4-dichloroanaline, 3,4-dichlorophenol and unmetabolized diuron also were detected.

Excretion

- Hodge et al. (1967) fed diuron (80% wettable powder) for 2 years to rats at dietary levels of 25 to 2,500 ppm and to dogs at dietary levels of 25 to 1,250 ppm. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day in rats and 0.025 mg/kg/day in dogs, this corresponds to doses of 1.25 to 125 mg/kg/day in rats and 0.625 to 31.25 mg/kg/day in dogs (Lehman, 1959). In rats, urinary excretion (6.3 to 492 ppm, depending on dose) was consistently greater than fecal excretion (1.0 to 204 ppm). In dogs, urinary excretion (6.3 to 307 ppm) was similar to fecal excretion (7.9 to 308 ppm). For both rats and dogs, combined urinary and fecal excretion accounted for only about 10% of the daily diuron ingestion.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of diuron in humans.

Animals

Short-term Exposure

- Acute oral LD_{50} values of 1,017 mg/kg and 3,400 mg/kg have been reported in albino rats by Boyd and Krupa (1970), NIOSH (1987) and Taylor (1976a), respectively. Signs of central nervous system depression were noted after treatment.

- Hodge et al. (1967) administered single oral doses of recrystallized diuron in peanut oil to male CR rats. The approximate lethal dose was 5,000 mg/kg, and the LD_{50} was 3,400 mg/kg. Survivors sacrificed after 14 days showed large and dark-colored spleens with numerous foci of blood.

- Hodge et al. (1967) administered oral doses of 1,000 mg/kg of recrystallized diuron five times a week for 2 weeks (10 doses) to six male CR rats. At necropsy, 3 or 11 days after the final dose, the spleens were large, dark and congested, and foci of blood were noted in both the spleen and bone marrow.

- Hodge et al. (1967) fed Wistar rats (five/sex/dose) diuron (purity not specified) in the diet for 42 days at dose levels of 0, 200, 400, 2,000, 4,000 or 8,000 ppm a.i. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 10, 20, 100, 200 or 400 mg/kg/day. Following treatment body weight, clinical chemistry, food consumption, hematology, 400 ppm (20 mg/kg/day) or less. At 2,000 ppm (100 mg/kg/day) or greater, red blood cell counts and hemoglobin values were decreased. A marked inhibition of growth occurred in the 4,000 ppm (200 mg/kg/day) or greater dosage groups, and there was increased mortality at 8,000 ppm. Based on these data, a No-Observed-Adverse-Effect Level (NOAEL) of 400 ppm (20 mg/kg/day) and a Lowest-Observed-Adverse-Effect Level (LOAEL) of 2,000 ppm (100 mg/kg/day) were identified.

Dermal/Ocular Effects

- Taylor (1976b) applied diuron to the intact or abraded skin of eight albino rabbits at dose levels of 1,000 to 2,500 mg/kg for 24 hours. After treatment, a slight erythema was observed, but no other symptoms of toxicity were noted during a 14-day observation period. The dermal LD_{50} was reported as >2,500 mg/kg.

- Larson (1976) applied technical diuron at doses of 1, 2.5, 5 or 10 mg/kg to intact abraded skin of New Zealand White rabbits for 24 hours. Adverse effects were not detected in exposed animals.

- In studies conducted by DuPont (no date), diuron (50% water paste) was not irritating to intact skin and was moderately irritating to abraded skin of guinea pigs. No data were available on skin sensitization. See also DuPont (1961).

- In studies conducted by Larson and Schaefer (1976), 10 mg of a fine dry powder of diuron was instilled into the conjunctival sac of one eye of each of six New Zealand White rabbits. Ocular irritation was not detected within 72 hours.

Long-term Exposure

- Hodge et al. (1967) fed albino Charles River rats (five/sex/dose) diuron (98% pure) for 90 days at dietary levels of 0, 50, 500 or 5,000 ppm. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 2.5, 25 or 250 mg/kg/day. Following treatment, body weight, food consumption, clinical chemistry and histopathology were evaluated. No adverse effects were observed in any parameter at 50 ppm. At 500 ppm there were no effects on males, but females gained less weight than controls and appeared cyanotic. At the 5,000-ppm dose level, body weights were reduced in both sexes, spleens were enlarged and exhibited hemosiderosis, and there was clinical and pathological evidence of chronic methemoglobinemia. Based on these data, a NOAEL of 50 ppm (2.5 mg/kg/day) and a LOAEL of 500 ppm (25 mg/kg/day) were identified.

- Hodge et al. (1967) fed diuron (80% wettable powder) to groups of Charles River rats (20/sex/dose) for 90 days at dietary levels of 0, 250 or 2,500 ppm a.i. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 12.5 or 125 mg/kg/day. At 2,500 ppm, both males and females ate less and gained less weight than did controls. There was a slight decrease in red blood cell count, more pronounced in females than in urinalysis and histology were evaluated. No effects were observed at males. No effect on food consumption or weight gain was noted at 250 ppm, but hematological changes were evident in females. This study identified a LOAEL of 250 ppm (12.5 mg/kg/day), the lowest dose tested.

- In a 2-year feeding study conducted by Hodge et al. (1964a, 1967), beagle dogs (two males/dose and three females/dose) were administered technical diuron (80% a.i.) in the diet at dose levels of 0, 25, 125, 250 or 1,250 ppm a.i. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to doses of diuron of 0, 0.625, 3.12, 6.25 or 31.25 mg/kg/day. Following treatment, body weight, clinical chemistry, hematology, organ weight, gross pathology and histopathology were evaluated. No adverse effects were reported at 25 ppm in any parameter measured. Abnormal blood pigment was observed at 125 ppm or greater. Hematological alterations (depressed red blood cells (RBC), hematocrit and hemoglobin) were observed at 250 ppm or greater. In the 1,250 ppm group, a slight weight loss occurred as well as increased erythrogenic activity in bone marrow and hemosiderosis of the spleen. Based on these data, a NOAEL of 25 ppm (0.625 mg/kg/day) and a LOAEL of 125 ppm (3.12 mg/kg/day) were identified.

- Hodge et al. (1964b, 1967) administered technical diuron (80% a.i.) in the diet of rats (35/sex/dose) for 2 years at dose levels of 0, 25, 125, 250 or 2,500 ppm a.i. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of diuron of 0, 1.25, 6.25, 12.5 or 125 mg/kg/day. Following treatment, body weight, clinical chemistry, hematology, food consumption, urinalysis, organ weights and histopathology were evaluated. No adverse effects were reported at 25 ppm (1.25 mg/kg/day) for any parameters measured. Abnormal blood pigments (sulfhemoglobin) were observed at 125 ppm (6.25 mg/kg/day) or greater. Hematological changes (decreased RBC, reduced hemoglobin), growth depression, hemosiderosis of the spleen and increased mortality were observed at 250 ppm (12.5 mg/kg/day) or greater. Based on these data, a NOAEL of 25 ppm (1.25 mg/kg/day) and a LOAEL of 125 ppm (6.25 mg/kg/day) were identified.

Reproductive Effects

- Hodge et al. (1964b, 1967) studied the effects of diuron (80% wettable powder) in a three-generation reproduction study in rats. Animals were supplied food containing 0 and 125 ppm a.i. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to a dose of 6.25 mg/kg/day. Fertility rate, body weight, hematology and histopathology were monitored. No effect was seen on any parameter except body weight, which significantly decreased in the F_{2b} and F_{3a} litters. A LOAEL of 125 ppm (6.25 mg/kg/day) was identified.

Developmental Effects

- Khera et al. (1979) administered by gavage a formulation containing 80% diuron at dose levels of 125, 250 or 500 mg of formulation per kg body weight to pregnant Wistar rats (14 to 18/dose) on days 6 through 15 of gestation. Vehicle (corn oil) controls (19 dams) were run concurrently. No maternal or teratogenic effects were observed at 125 mg/kg/day. Developmental effects appeared to increase in all treatment groups, i.e. wavy ribs, extra ribs and delayed ossification. The incidence of wavy ribs was statistically significant at 250 mg/kg ($p < 0.05$) and greater. Maternal and fetal body weights decreased significantly at 500 mg/kg ($p < 0.05$). A NOAEL was not determined from this study for fetotoxic effects; hence, a LOAEL of 125 mg/kg of formulation per day was identified.

Mutagenicity

- Andersen et al. (1972) reported that diuron did not exhibit mutagenic activity in T_4 bacteriophage test systems (100 ug/plate) or in tests with eight histidine-requiring mutants of *Salmonella typhimurium* (small crystals applied directly to surface of plate).

- Fahrig (1974) reported that diuron (purity not specified) was not mutagenic in a liquid holding test for mitotic gene conversion in *Saccharomyces cerevisiae*, in a liquid holding test for forward mutation to streptomycin resistance in *Escherichia coli*, in a spot test for back mutation in *S. marcescens* or in a spot test for forward mutation in *E. coli*.

- Recent studies by DuPont (1985) did not detect evidence of mutagenic activity for diuron in reversion tests in several strains of *S. typhimurium* (with or without metabolic activation), in a Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward gene mutation test or in unscheduled DNA synthesis tests in primary rat hepatocytes. However, in an *in vivo* cytogenetic test in rats, diuron was observed to cause clastogenic effects.

Carcinogenicity

- Hodge et al. (1964b, 1967) fed Wistar rats (35/sex/dose) diuron (80% wettable powder) in the diet at levels of 0, 25, 125, 250 or 2,500 ppm a.i. for 2 years. Assuming that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 1.25, 6.25, 12.5 or 125 mg/kg/day. There was some early mortality in males at 250 and 2,500 ppm, but the authors ascribed this to viral infection. Histological examination of tissues showed no evidence of changes related to diuron; however, only 10 animals or fewer were examined per group. Tumors and neoplastic changes observed were similar in exposed and control groups, and the authors concluded there was no evidence that diuron was carcinogenic in rats.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable information was found in the available literature for use in the determination of the One-day HA value for diuron. It is, therefore, recommended that the Ten-day HA value for a 10-kg child, calculated below as 1.0 mg/L (1,000 ug/L) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Khera et al. (1979) has been selected to serve as the basis for the Ten-day HA for diuron. In this study, pregnant rats were administered diuron (80%) on days 6 through 15 of gestation at dose levels of 0, 125, 250 or 500 mg/kg/day. Developmental effects appeared to increase in the diuron-treated groups as compared to the control group, i.e. wavy ribs, extra ribs and delayed ossification. The incidence of wavy ribs was statistically significant at 250 mg/kg/day ($p < 0.05$). Fetal and maternal body weights were decreased at 500 mg/kg ($p < 0.05$). A NOAEL was not determined from this study at the lowest dose tested (LDT) based on developmental toxicity; hence, the LOAEL for this study was 125 mg/kg/day (LDT).

Using a LOAEL of 125 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-Day HA} = \frac{(125 \text{ mg/kg/day}) \ (10 \text{ kg}) \ (0.80)}{(1{,}000) \ (1 \text{ L/day})} = 1.0 \text{ mg/L } (1{,}000 \text{ ug/L})$$

where:

125 mg/kg/day = LOAEL, based on fetotoxicity in rats exposed to diuron via the diet for days 6 through 15 of gestation.

10 kg = assumed body weight of a child.

0.80 = correction factor to account for 80% active ingredient.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The 90-day feeding study in rats by Hodge et al. (1967) has been chosen to serve as the basis for determination of the Longer-term HA values for diuron. In this study, five animals per sex were fed diuron (98% pure) at dose levels of 0, 2.5, 25 or 250 mg/kg/day. Based on decreased weight gain and methemoglobinemia, this study identified a NOAEL of 2.5 mg/kg/day and a LOAEL of 25 mg/kg/day. These values are supported by the 42-day feeding study of Hodge et al. (1964b), in which a NOAEL of 20 mg/kg/day and a LOAEL of 100 mg/kg/day were identified. This study was not selected, however, since the duration of exposure was only 42 days.

Using a NOAEL of 2.5 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(2.5\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.25\ \text{mg/L}\ (300\ \text{ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of effects on weight gain or blood chemistry in rats exposed to diuron via the diet for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(2.5\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 0.875\ \text{mg/L}\ (900\ \text{ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of effects on weight gain or blood chemistry in rats exposed to diuron via the diet for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in dogs by Hodge et al. (1964a, 1967) has been selected to serve as the basis for estimating the Lifetime HA for diuron. In this study, dogs (2 to 3/sex/dose) were fed diuron at doses of 0.625, 3.12, 6.25 or 31.15 mg/kg/day of active ingredient. Hematological alterations were observed at 3.12 mg/kg/day or greater, and this was identified as the LOAEL. No effects were reported at 0.625 mg/kg/day in any parameter measured, and this was identified as the NOAEL. This value is supported by a lifetime study in rats by the same authors (Hodge et al., 1964b). In this study, rats were fed diuron at dose levels of 0, 1.25, 6.25, 12.5 or 125 mg/kg/day for 2 years. Hematological changes were observed at 6.25 mg/kg/day or greater, and a NOAEL of 1.25 mg/kg/day was identified.

Using a NOAEL of 0.625 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.625 \text{ mg/kg/day})}{(100)\ (3)} = 0.002 \text{ mg/kg/day}$$

where:

0.625 mg/kg/day = NOAEL, based on absence of hematological effects in dogs exposed to diuron via the diet for 2 years.

100 = uncertainty factor chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = additional uncertainty factor. This factor is used to account for a lack of adequate chronic toxicity studies in the data base preventing establishment of the most sensitive toxicological end point.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.002 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.07 \text{ mg/L } (70 \text{ ug/L})$$

where:

0.002 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.07 \text{ mg/L})\ (20\%) = 0.014 \text{ mg/L } (10 \text{ ug/L})$$

where:

0.07 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Hodge et al. (1964b, 1967) fed rats (35/sex/dose) diuron in the diet at ingested doses of up to 125 mg/kg/day for 2 years. Histological examinations did not reveal increased frequency of tumors; however, fewer than half of the survivors were examined.
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of diuron.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), diuron may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

- A structurally related analogue of diuron (i.e., linuron) appears to reflect some oncogenic activity. In addition, a Russian study by Rubenchik et al. (1973) reported gastric carcinomas and pancreatic adenomas in rats (strain not designated) given diuron at 450 mg/kg/day for 22 months. However, the actual data for the study are unavailable for Agency review.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- An Acceptable Daily Intake (ADI) of 0.002 mg/kg/day, based on a NOAEL of 0.625 mg/kg from a dog study and an uncertainty factor of 300 has been calculated (U.S. EPA, 1986b).

- Residue tolerances that range from 0.1 to 7 ppm have been established for diuron in or on agricultural commodities (U.S. EPA, 1985).

VII. ANALYTICAL METHODS

- Analysis of diuron is by a high-performance liquid chromatographic (HPLC) method applicable to the determination of certain carbamate and urea pesticides in water samples (U.S. EPA, 1986c). This method requires a solvent extraction of approximately 1 L of sample with methylene chloride using a separatory funnel. The methylene chloride extract is dried and concentrated to a volume of 10 mL or less. HPLC is used to permit the separation of compounds, and the measurement is conducted with an ultraviolet (UV) detector. The method has been validated in a single laboratory and the estimated detection limit for diuron is 0.07 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) and powdered activated carbon (PAC) adsorption and chlorination effectively remove diuron from water.

- El-Dib and Aly (1977b) determined experimentally the Freundlich constants for diuron on GAC. Although the values do not suggest a strong adsorption affinity for activated carbon, diuron is better adsorbed than other phenylurea pesticides.

- El-Dib and Aly (1977b) calculated, based on laboratory tests, that 66 mg/L of PAC would be required to reduce diuron concentration by 98%, and 12 mg/L of PAC to reduce diuron concentration by 90%.

- Conventional water treatment techniques of coagulation with ferric sulfate, sedimentation and filtration proved to be only 20% effective in removing diuron from contaminated water (El-Dib and Aly, 1977a). Aluminum sulfate was reportedly less effective than ferric sulfate.

- Oxidation with chlorine for 30 minutes removed 70% of diuron at a pH 7. Under the same conditions, 80% of diuron was oxidized by chlorine dioxide (El-Dib and Aly, 1977a). Chlorination, however, will produce several degradation products whose environmental toxic impact should be evaluated prior to selection of oxidative chlorination for treatment of diuron-contaminated water.

- The treatment technologies cited above for the removal of diuron from water are available and have been reported to be effective. However, selection of an individual technology or combinations of technologies to attempt diuron removal from water must be based on a case-by-case technical evaluation and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

ENDOTHALL

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

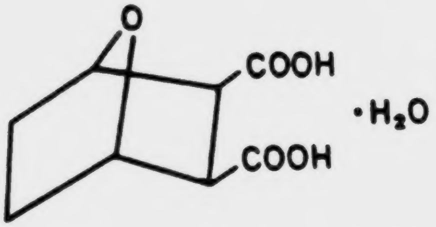
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 145-73-3

Structural Formula



7-Oxabicyclo-(2,2,1)-heptane-2,3-dicarboxylic acid

Synonyms

- 1,2-dicarboxy3,6-endoxocyclohexane; Aquathol K; Hydrothol 191; Hydrothol 191 Granular; Endothall Truf Herbicide; Herbicide 273; Des-i-cate; Accelerate (Meister, 1988).

Uses

- Preemergence and postemergence herbicide, defoliant, dessicant, aquatic algicide, growth regulator (Meister, 1988).

Properties (Reinert and Rogers, 1984; Neely and Mackay, 1982; Chiou et al., 1977; Carlson et al., 1978; Simsiman et al., 1976)

Chemical Formula	$C_8H_{10}O_5$
Molecular Weight	186.06
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	144°C to the anhydride
Density	--
Vapor Pressure (25°C)	Negligible
Specific Gravity	--
Water Solubility (25°C)	100 g/L (acid monohydrate) 1.228 g/L (dipotassium salt)
Log Octanol/Water Partition Coefficient	1.91 (acid) 1.36 (dipotassium salt)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Endothall was not found in any of the 3 surface water or 604 ground water samples analyzed that were taken from 2 surface water locations and 600 ground water locations (STORET, 1988). This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out

of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- The low K_{ow} values indicate that endothall would not significantly partition to sediments. K_{oc} values for equilibrium sorption studies using the dipotassium salt were 110 and 138 for sidiment-water systems from a small eutrophic pond and oligomesotrophic reservoir, respectively (Reinert and Rodgers, 1984). An overall K_p value of 0.958 was calculated from this study which compares favorably with K_p values for the acid ranging from 0.41 to 0.9 calculated from a flask system containing Lake Tomahawk water and sediment (Simsiman and Chesters, 1975). A K_p value of approximately 0.4 was calculated from the data presented by Sikka and Rice (1973) in which a Syracuse, NY farm pond was treated with dipotassium endothall. Therefore, sorption would not be considered a significant environmental fate process for endothall in the environments studied.

- Endothall has been shown to not significantly bioconcentrate. In laboratory and field studies, consistently low endothall levels have been observed. A BCF for endothall in mosquito fish (Gambusia affinis) of 10 was observed in a modified Metcalf model ecosystem (Isensee, 1976). In a field study by Serns (1977), a 5 mg/L dipotassium endothall concentration resulted in BCF values in bluegills ranging from 0.003 to 0.008. After 72 hr, fish flesh residues were not detectable. Endothall residues in caged bluegills were consistently below the minimum detectable level of 0.1 mg/kg in a rservoir study by Reinert and Rodgers (1986). Similar results were seen after an application of the diamine salt (Walker, 1963). Comparable fish BCF values calculated from regression equations were 0.65 (Neely et al., 1974) and 1.05 (Chiou et al., 1977).

- Some organisms will exhibit temporary endothall residues that exceed the water concentration by more than an order of magnitude. Isensee (1976) observed BCF values of 150 for the water flea, 63 for green alga (Oedogonium), and 36 for a snail (Physa); however, the endothall concentrations with the organisms were transient and were not passed along trophic levels. A BCF of 0.73 was calculated for the dipotassium salt of endothall in duckweed (Lemna minor) using the endothall K_{ow} and the regression equation found in Lockhart et al. (1983).

- Volatilization, hydrolysis, and oxidation are not significant fate processes affecting the persistence of endothall in aquatic environments (Reinert and Rodgers, 1984). Endothall is also not subject to photochemical degradation. In a laboratory study using the disodium salt of endothall, no degradation was observed when a lamp of 254 nm wavelength was employed (Mitchell, 1961).

- Biotransformation and biodegradation are the dominant fate processes affecting the persistence of endothall in aquatic environments (Simsiman and Chesters, 1975; Holmberg and Lee, 1976; Simsiman et al., 1976). A biotransformation half-life of 8.35 d was observed in a shake-flask study using three [^{14}C]endothall concentrations and water from an oligomesotrophic reservoir (Reinert et al., 1986). Overall aqueous decay rates are considered a good estimate of endothall biotransformation in that other fate processes are insignificant. Keckemet (1980) observed an aqueous endothall half-life of about 6.7 d after a review of the literature. The persistence of both the dipotassium and amine salts was less than 7 d in Gatan Lake. Panama Canal (Gangstad, 1983a). A half-life for the dipotassium salt of 7.3 d was calculated from field studies using farm ponds (Yeo, 1970). Reinert et al. (1985) observed 4.1 d endothall half-life in 133 L plastic greenhouse pools containing water, sediment, and Eurasian watermilfoil. Dipotassium endothall half-lives in a marginally treated north Texas reservoir ranged from 1.1 to 1.2 days (Rodgers et al., 1984; Reinert and Rodgers, 1986). The results presented in Holmberg and Lee (1976) compare favorably with the above endothall half-lives. A 4.1 d half-life was calculated from a Wisconsin pond treated with dipotassium endothall.

- Endothall persistence in sediments ranged from 0 to 7 d in work reported by Keckemet (1980) and less than 4 d after a nominal 2 mg/L dosage in a Texas reservoir (Rodgers et al., 1984; Reinert and Rodgers, 1986). Gangstad (1983a) observed endothall persistence in Gatan Lake sediment <3 d for the dipotassium salt, but >21 d for the amine salt when treated with 2 mg/L. In a pond study, Langeland and Warner (1986) observed an overall endothall (Aquathol® K) persistence of 26 d after an initial concentration of 2.1 mg/L.

III. PHARMACOKINETICS

Absorption

- Few data exist regarding endothall pharmacokinetics in mammals. Soo et al. (1967) performed pharmacokinetic experiments with male and female Wistar rats. Taking ^{14}C levels in urine and exhaled air as a crude estimate of absorption, approximately 10% of a 5 mg/kg oral dose of ^{14}C-labeled (at carbons 1 or 2 of the ring) endothall (dissolved in 20% ethanol to a concentration of 1 mg/mL) was absorbed by the rats within 72 hours. The rats had received 5 mg/kg of unlabeled endothall in the diet for 2 weeks prior to treatment with ^{14}C-endothall. Endothall measurements in this study were as ^{14}C label.

- Deaths in rabbits directly exposed to endothall in the eye or on the skin (Pharmacology Research, Inc, 1975a, 1975b) indicate the potential for absorption by these routes.

Distribution

- In the Soo et al. (1967) study, the absorbed endothall was distributed in low levels through most body tissues. Peak levels in all tissues were observed 1 hour after dosing, with most of the dose (about 95%) found in the stomach and intestine. Otherwise, the tissues with the highest concentrations after 1 hour were the liver and kidney (1.1 and 0.9% respectively), with lower concentrations (0.02 to 0.1%) in heart, lung, spleen and brain. Very low concentrations were observed in muscle, and endothall was not detected in fat. No marked preferential accumulation was apparent.

Metabolism

- The metabolism of endothall is not known to be characterized.

Excretion

Soo et al. (1967) described excretion as follows:

- Clearance of ^{14}C-endothall was biphasic in the stomach ($t_{1/2}$ = 2.2 and 14.2 hours) and kidney ($t_{\frac{1}{2}}$ = 1.6 and 34.6 hours) and monophasic in the intestine and liver ($t_{\frac{1}{2}}$ = 14.4 and 21.6 hours, respectively). Total excretion of the ^{14}C label was over 95% complete by 48 hours and over 99% complete by 72 hours, suggesting that no significant bioaccumulation occurred.
- Approximately 90% of the administered dose was excreted in the feces. Urinary excretion accounted for approximately 7% of the dose, and approximately 3% of the radioactive label was recovered in expired carbon dioxide.
- Recycling of endothall by biliary circulation was ruled out as a major excretory route because ^{14}C activity in liver was small relative to that in the original dose.
- Approximately 20% of the dose excreted in the feces was unchanged endothall with the remaining radioactivity presumed to be an endothall conjugate.
- Soo et al. (1967) also found no radioactivity in pups from lactating dams given oral doses of ^{14}C-endothall.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of endothall in humans except for one case history of a young male suicide victim who ingested an estimated 7 to 8 g of disodium endothall in solution (approximately 100 mg endothall ion/kg). Repeated vomiting was evident. Autopsy revealed focal hemorrhages and edema in the lungs and gross hemorrhage of the gastrointestinal (GI) tract (Allender, 1983).

Animals

Short-term Exposure

- Early acute studies report cardiac arrest (Goldstein, 1952) or respiratory failure (Srensek and Woodard, 1951) as causes of death in dogs and rabbits. Endothall was injected intravenously in both studies with these effects observed at doses of 5 mg/kg (lowest) and higher.

- The available acute oral dose studies are essentially restricted to mortality data without biochemical or histopathological observations. The acute toxicity of endothall acid appeared to be greater than that of the salt forms normally used in herbicide formulations. In rats, the oral LD_{50} of endothall was reported as 35 to 51 mg/kg for the acid form and 182 to 197 mg/kg for the sodium salt (Simsiman et al., 1976; Tweedy and Houseworth, 1976).

- Rats were given 1,000 or 10,000 ppm disodium endothall in the diet (Brieger, 1953a) and doses were calculated by assuming a body weight of 0.4 kg and daily food consumption of 20 g. Slight liver degeneration and focal hemorrhagic areas in the kidney were reported for male and female rats dosed orally with approximately 40 mg endothall ion/kg/day for 4 weeks; most of the rats receiving approximately 400 mg endothall ion/kg/day died within 1 week.

- Nine male dogs (one dog/dose) were dosed orally with capsules containing 1 to 50 mg disodium endothall/kg/day (0.8 to 40 mg endothall ion/kg/day) for 6 weeks (Brieger, 1953b). All dogs that were administered 20 to 50 mg disodium endothall/kg/day died within 11 days. Vomiting and diarrhea were observed in the group given 20 mg disodium endothall/kg/day. Pathological changes in the GI tract, described as congested and edematous stomach walls and edematous upper intestines, were indicated as common in all dogs. Erosion and hemorrhages in the stomach were observed with doses of 20 mg/kg/day or more.

Dermal/Ocular Effects

- Goldstein (1952) reported that a 1% solution of endothall applied to the unbroken skin of rabbits produced no effects. The same solution applied to scarified skin resulted in mild skin lesions. Ten to twenty percent solutions or applications of the pure, powdered material to intact or scarified skin resulted in more severe damage, including necrosis, and the deaths of some treated animals.

- Topical exposure of six rabbits to 200 mg endothall technical/kg resulted in the death of all rabbits within 24 hours (Pharmacology Research, Inc., 1975a).

- Technical endothall (0.1 g equivalent to 80 mg endothall ion) produced severe eye irritation in three rabbits when directly applied to the conjunctiva. Effects included corneal opacity, conjunctival irritation and iridic congestion. Furthermore, technical endothall apparently produced systemic effects by this route of absorption, since several animals died within 24 hours as a result of this exposure. Eyes were rinsed with water 20 to 30 seconds after treatment in three rabbits; conjunctival irritation and iridic congestion reversed in 4 days in two rabbits but persisted along with corneal opacity in one rabbit for 7 days (Pharmacology Research, Inc., 1975b).

Long-term Exposure

- Beagle dogs (four/sex/group) fed diets containing 0, 100, 300 or 800 ppm disodium endothall (equivalent to 0, 2, 6 or 16 mg endothall ion/kg/day for 24 months showed no gross signs of toxicity (Keller, 1965). Values for hematology, urinalysis, weight gain and food consumption were within normal limits and comparable to those for control animals. Increased stomach and small intestine weights were observed in the intermediate and high-dose groups. However, microscopic examination of essentially all tissues in the high-dose group revealed no pathological changes that could be attributed to endothall ingestion. A No-Observed-Adverse-Effect Level (NOAEL) of 2 mg endothall ion/kg/day is identified from this study.

- Brieger (1953b) reported no toxic effects in female rats given dietary levels as high as 2,500 ppm disodium endothall (about 100 mg endothall ion/kg/day, assuming food intake of 20 g/day and mean body weight of 0.4 kg) for 2 years.

Reproductive Effects

- A three-generation study in rats was reported by Scientific Associates (1965). Groups of male and female rats were fed diets containing 0, 100, 300 or 2,500 ppm disodium endothall (equivalent to 0, 4, 12 or 100 mg endothall ion/kg/day) until they were 100 days old and were then mated. Three successive generations of offspring were maintained on the test diet for 100 days and then bred to produce the next test generation. Pups in the 4-mg/kg/day dose group were normal, pups in the 12-mg/kg/day group had decreased body weights at 21 days of age and pups in the 100 mg/kg/day group did not survive more than 1 week. A NOAEL for reproductive effects of 4 mg endothall ion/kg/day was identified from this study.

Developmental Effects

- A short-term teratology study in rats by Science Applications, Inc. (1982) indicated no observable signs of developmental toxicity at dose levels that were fatal to the dams. This study suggests that the dams are more susceptible to endothall than are the embryos or fetuses. Groups of 25 or 26 female rats were mated and then orally dosed with 0, 10, 20 or 30 mg/kg/day of aqueous endothall technical (0, 8, 16 or 24 mg endothall ion/kg/day) on days 6 to 19 of gestation. Two dams died from the 20-mg/kg/day dose, and 10 dams died from the 30-mg/kg/day dose. No clinical signs were noted prior to death, and no lesions were observed at necropsy. The researchers concluded that endothall technical was not embryotoxic or teratogenic at maternal doses of 30 mg/kg/day or below. A NOAEL of 10 mg endothall technical/kg/day based on maternal effects was identified.

Mutagenicity

- Mutagenicity results from short-term in vitro tests are mixed, with various forms of endothall reported as test agents. Mutagenicity studies utilizing Salmonella with and without metabolic activation resulted in negative findings for endothall technical (Andersen et al., 1972; Microbiological Associates, 1980a). Mutagenic activity was not found in BALB/3T3 Clone A31 mouse cells exposed to endothall technical (Microbiological Associates, 1982b).

- For the following studies, Wilson et al. (1956) used "commercial Endothall" with no further description, whereas the remaining investigators used Aquathol K, a commercial formulation containing dipotassium endothall at a level of 28.6% acid equivalent. In Drosophila melanogaster, mutagenic results were mixed, with Wilson et al. (1956) and Sandler and Hamilton-Byrd (1981) reporting positive and negative results, respectively. Sandler and Hamilton-Byrd (1981) reported negative results in a mutagenicity assay with the mold Neurospora crassa. A sister chromatid exchange study in human lymphocytes was negative (Vigfusson, 1981). Transformation was induced in a BALB/c 3T3 test for malignant transformation (Litton Bionetics, Inc., 1981).

Carcinogenicity

- No statistically significant numbers or types of tumors were observed in rats fed as much as 100 mg endothall ion/kg/day for 2 years (Brieger, 1953b).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs)* are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

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*Because the test material in the various toxicity studies was salt or acid forms of endothall, the HAs described herein are expressed in terms of endothall ion.

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No studies were located in available literature that were suitable for calculation of the One-day HA. The single-dose studies measured mortality as the toxicological end point and are not suitable for use in calculating an HA. The value of 0.8 mg/L calculated as the Ten-day HA can be used as a conservative estimate of the One-day HA.

Ten-day Health Advisory

The teratology study by Science Applications, Inc. (1982) has been selected as the basis for the Ten-day HA. It is the only study that defined a short-term NOAEL (8 mg endothall ion/kg/day, based on maternal toxicity).

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(8\text{ mg/kg/day})\ (10\text{ kg})}{(100)\ (1\text{ L/day})} = 0.8\text{ mg/L } (800\text{ ug/L})$$

where:

8 mg/kg/day = NOAEL based on the absence of fetal and maternal effects in rats exposed to endothall acid orally for 13 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

There is concluded to be insufficient data for calculation of a Longer-term HA. Therefore, the DWEL adjusted for a 10-kg child (0.2 mg/L) is proposed as a conservative estimate for a Longer-term HA.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classifed as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in dogs by Keller (1965), which identified a NOAEL of 2 mg endothall ion/kg/day, has been selected to serve as the basis for the Lifetime HA for endothall. The study by Scientific Associates (1965) was of shorter duration (100 days/generation) and did not as completely define a NOAEL (except for 4 mg endothall ion/kg/day for reproductive effects); however, the NOAEL in this study approximates that in the Keller (1965) study. The 2-year study in rats by Brieger (1953b) showed no adverse effects from doses up to 100 mg endothall ion/kg/day, but no information was provided on the parameters tested and the levels at which effects did occur.

Using the NOAEL of 2 mg/kg/day, the Lifetime HA for endothall is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(2\ \text{mg/kg/day})}{(100)} = 0.02\ \text{mg/kg/day}$$

where:

2 mg/kg/day = NOAEL, based on absence of increased organ weight and organ-body weight ratios in the stomach and small intestine in dogs exposed to endothall in the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.02\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.7\ \text{mg/L}\ (700\ \text{ug/L})$$

where:

0.02 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.7 \text{ mg/L})\ (20\%) = 0.14 \text{ mg/L}\ (100 \text{ ug/L})$$

where:

0.7 mg/L = DWEL.

20% = assumed percentage of daily exposure contributed by ingestion of drinking water.

Evaluation of Carcinogenic Potential

- Available toxicity data do not show endothall as carcinogenic.
- Endothall can be placed in Group D (inadequate evidence in humans and animals) by the EPA's guidelines for carcinogenic risk assessment (U.S. EPA, 1986).
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of endothall (WHO, 1982).

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- An interim tolerance of 200 ug/L has been published for residues of endothall, used to control aquatic plants, in potable water (CFR, 1979).
- Residue tolerances for endothall published by the U.S. EPA (CFR, 1977) include 0.1 ppm in or on cottonseed, 0.1 ppm in or on potatoes, 0.05 ppm in or on rice grain and 0.05 ppm in or on rice straw.
- A tolerance is a derived value based on residue levels, toxicity data, food consumption levels, hazard evaluation and scientific judgment; it is the legal maximum concentration of a pesticide in or on a raw agricultural commodity or other human or animal food (Paynter et al., undated).
- The ADI set by the U.S. EPA Office of Pesticide Programs is 0.02 mg/kg/day based on the 2 mg/kg/day NOAEL in the 2-year dog study by Keller (1965) and a 100-fold uncertainty factor.

VII. ANALYTICAL METHODS

- Endothall is a dicarboxyllic herbicide used to control aquatic vegetation. It presents a difficult analytical challenge since its highly polar structure does not allow simple solvent extraction from water. It lacks any elements which would allow use of the selective detectors commonly used in pesticide analysis. To obtain any sensitivity chemical derivatization is required both for detection and concentration of the extract.

A draft method has been developed by EMSL-CI (U.S. EPA, 1988) which allows a small volume of sample to be derivatized with pentafluorophenylhydrazine (PFPH), and cleaned up by solid phase absorbant-extraction. Analysis is by electron-capture gas chromatography. The single laboratory estimated detection limit is 9.1 ug/L. The single operator recovery and precision for this method in tap water is 69% and 4%, respectively.

VIII. TREATMENT TECHNOLOGIES

- No information was found in the available literature on treatment technologies capable of effectively removing endothall from contaminated water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

ETHYLENE THIOUREA

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

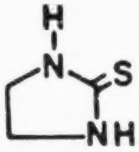
II. GENERAL INFORMATION AND PROPERTIES

Ethylene thiourea (ETU) is no longer used in commerce but is a common degradation product of the ethylene bisdithiocarbamate (EBDC) pesticides.

Although the toxicity of ETU may be similar to the toxic effects observed with the EBDCs, the One-day, Ten-day, Longer-term and Lifetime HAs for ETU should not necessarily be considered protective of exposure to individual EBDCs at this time. The mechanisms of toxicity for these substances are still under evaluation.

CAS No. 96-45-7

Structural Formula



2-Imidazolidinethione

Synonyms

- ETU

Uses

- Degradation product of several EBDC pesticides.

Properties

Chemical Formula	$C_3H_6N_2S$
Molecular Weight	102.2
Physical State (25°C)	White crystals
Boiling Point	--
Melting Point	203°
Density	—
Vapor Pressure	—
Specific Gravity	--
Water Solubility (30°C)	20 g/L
Log Octanol/Water Partition Coefficient	—
Taste Threshold	—
Odor Threshold	--

Occurrence

- ETU was not found in sampling performed at 264 ground water stations, according to the STORET database (STORET, 1988).

Environmental Fate

- Ethylene thiourea can be degraded by photolysis (U.S. EPA, 1982).

- ^{14}C-Ethylene thiourea was intermediately mobile (R_f 0.61) to very mobile (R_f 1.00) in muck and sandy loam soils, respectively, as determined by soil TLC (U.S. EPA, 1986a). Adsorption was correlated to organic matter. Following 6 days of incubation in dry silty clay loam soil, ETU residues were immobile; however, ETU residues subjected to a wet-dry cycle were slightly mobile (R_f 0.2).

- Levels of ETU (purity unspecified) declined at an unspecified rate in sand, with a half-life of 1-6 days (U.S. EPA, 1986a). Concentrations of ETU declined from 220 ppm at day 0 to 116 ppm by day 1 and 86 ppm by day 6.

- Mancozeb has been shown to have a half-life of less than 1 day in sterile water before degrading to ETU (U.S. EPA, 1982). The ethylene bisdithiocarbamates (EBDCs) are generally unstable in the presence of moisture and oxygen, and the EBDCs decompose rapidly in water as well as in biological systems (U.S. EPA, 1982).

- The EBDCs decompose rapidly in water. Mancozeb has been shown to have a half-life of less than 1 day in sterile water before degrading to ETU (U.S. EPA, 1982).

- Photolysis is a major degrading pathway for ETU (U.S. EPA, 1982).

III. PHARMACOKINETICS

Absorption

- Allen et al. (1978) reported a very high rate of absorption of ^{14}C-ETU gastrically administered at 40 mg/kg to female rhesus monkeys and female Sprague-Dawley rats. In both species, feces accounted for less than 1.5% of the excreted radioactivity at 48 hours after administration.

- Absorption was also high in male Sprague-Dawley rats orally administered ^{14}C-ETU at 4 mg/kg, with 82.7% of the total administered dose detected in the urine at 24 hours (Iverson et al., 1980).

Distribution

- Allen et al. (1978) reported that in rhesus monkeys administered ^{14}C-ETU at 40 mg/kg by gastric intubation, total tissue distribution at 48 hours was approximately 25% of the administered dose; approximately half of that was concentrated in muscle, with measurable amounts noted in blood, skin and liver. In Sprague-Dawley rats, however, total tissue distribution was less than 1% of the administered dose.

- Except in the thyroid, ETU was not found to accumulate in rats given an oral dose (amount not specified) (U.S. EPA, 1982). Up to 80% of the absorbed dose was eliminated in the urine 24 hours after administration.

Metabolism

- Iverson et al. (1980) identified the 24-hour urinary metabolites of ^{14}C-ETU orally administered to male Sprague-Dawley rats at 4 mg/kg. Imidazoline was present at 1.9% of the total recovered dose, imidazolone at 4.9%, ethylene urea at 18.3% and unchanged ETU at 62.6%. In female cats, intravenous (iv) administration of this dose resulted in unchanged ETU present in the urine at only 28% of the total recovered dose, with S-methyl ETU at 64.3% and ethylene urea at 3.5%.

- One hundred percent of the ETU (dose not specified) fed to mice was recovered rapidly (time not specified) with 50% recovered in the urine (U.S. EPA, 1982). Of the urinary products, 52% was unchanged ETU, 12% was ethylene urea, and 37% were polar products.

- All animals that have been tested appear to metabolize EBDCs rapidly. ETU and ethylene bisdiisothiocyanato sulfide (EBIS) are the major metabolites formed (U.S. EPA, 1982). Approximately 7% of an EBDC dose is converted to ETU in vivo in the rat and 2% in the mouse (Nelson, 1987; Jordan and Neal, 1979).

Excretion

- Allen et al. (1978) reported that 48 hours after gastric administration of ^{14}C-ETU at 40 mg/kg to rhesus monkeys, approximately 55% of the administered dose was detected in the urine and 0.5% in the feces. In Sprague-Dawley rats dosed identically, 82% was recovered in the urine and 1.3% in the feces.

- Iverson et al. (1980) reported that 82.7 and 80.6% of the total radioactivity of a single 4-mg/kg dose of ^{14}C-ETU was eliminated in the 24-hour urine of orally treated male Sprague-Dawley rats and iv-treated female cats, respectively.

IV. HEALTH EFFECTS

Humans

- No suitable information was found in the available literature on the health effects of ETU in humans.

Animals

Short-term Exposure

- The acute oral LD_{50} for ETU is 1,832 mg/kg in rats (U.S. EPA, 1982).

- Graham and Hansen (1972) measured ^{131}I uptake in male Osborne-Mendel rats administered ETU (purity not stated) in the diet at 50, 100, 500 or 750 ppm for various time periods (e.g., 30, 60, 90 or 120 days). Assuming that 1 ppm in the diet of younger rats is equivalent to approximately 0.1 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 5, 10, 50 or 75 mg/kg/day. Four hours after the injection of ^{131}I, uptake was decreased significantly in rats that had ingested ETU at 500 or 750 ppm for all time periods. At 24 hours after ^{131}I injection, uptake was significantly decreased in rats that had ingested 100, 500 or 750 ppm for all time periods. Histologically, the thyroid glands of rats ingesting ETU at approximately 5.0 mg/kg, the No-Observed-Adverse-Effect Level (NOAEL) for this study, were not different from those of control rats. There was slight hyperplasia of the thyroid in rats given 100 ppm (10 mg/kg/day). At doses of 500 or 750 ppm (50 or 75 mg/kg/day), the thyroid had moderate to marked hyperplasia.

- In an 8-day maximum tolerated dose (MTD) study by Plasterer et al. (1985), dose levels of 0, 75, 150, 300, 600 and 1,200 mg/kg ETU were given by gavage to mice (10/group, sex not specified). Body weight and mortality were evaluated. No significant effects were noted on body weight at the end of the eighth day. Based on mortality, ETU was considered moderately toxic by the authors. An MTD of 600 mg/kg was determined.

- In a study by Freudenthal et al. (1977), ETU (>95% pure) was fed to rats (20/sex/group) in the diet at levels of 0, 1, 5, 25, 125 or 625 ppm for 30 days. Assuming that 1 ppm in the diet of a young rat is equivalent to 0.1 mg/kg (Lehman, 1959), these levels correspond to doses of about 0, 0.1, 0.5, 2.5, 12.5 or 62.5 mg/kg. Thyroid function, food consumption, body weight gain and histopathology were assessed in the animals. Rats in the 625-ppm groups showed signs of toxicity after 8 days of exposure. Hair loss, dry skin, increased salivation and decreased food consumption and body weight gain were observed. Other effects noted in the 625-ppm dose group were decreased iodine uptake and percent triiodothyronine (T_3) bound to thyroglobulin. Thyroid-stimulating hormone (TSH) was increased, and T_3 and thyroxine (T_4) decreased in the 625-ppm dose group. Thyroid hyperplasia was also noted in this group. Animals exposed to 125 ppm exhibited increased TSH; decreased T_4, and thyroid hyperplasia. Other thyroid parameters were not affected. Based on the absence of adverse effects in rats exposed to 25 ppm or less after 30 days, a NOAEL of 25 ppm (2.5 mg/kg) was identified.

- Arnold et al. (1983) showed that the thyroid effects of ETU (purity not stated) administered in the diet for 7 weeks to male and female Sprague-Dawley rats were reversible when ETU was removed from the diet. Dose-related significant decreases in body weight and increases in thyroid weight were observed in all treated animals, starting at dose levels of 75 ppm (approximately 7.5 mg/kg/day based on Lehman, 1959). This dose was identified as the Lowest-Observed-Adverse-Effect Level (LOAEL) for this study.

- In a 60-day study, which was a continuation of the above study by Freudenthal et al. (1977), 14/40 rats in the 625-ppm group died. Thyroid hyperplasia and altered thyroid function were observed in the two high-dose groups. Thyroid hyperplasia was also observed in the 25-ppm group. This effect, however, was not observed in this dose group when exposure was continued to 90 days. Thus, the NOAEL for this study is presumed to be 25 ppm, or 2.5 mg/kg.

Dermal/Ocular Effects

- No information was found in the above literature on the dermal/ocular effects of ETU.

Long-term Exposure

- Freudenthal et al. (1977) described alterations in thyroid function and changes in thyroid morphology when Sprague-Dawley rats were administered ETU (96.8% pure) in the diet at levels of 1 to 625 ppm (approximately 0.1 to 62.5 mg/kg/day based on Lehman, 1959) for up to 90 days. The NOAEL was reported to be 19.5 mg/kg/day at week 1 and 12.5 mg/kg/day at week 12.

- Graham and Hansen (1972) measured ^{131}I uptake in male Osborne-Mendel rats administered ETU (purity not specified) in the diet at 50, 100, 500 or 750 ppm for up to 120 days. Assuming that 1 ppm in the diet of older rats is equivalent to approximately 0.05 mg/kg/day (Lehman, 1959), these dosages are equivalent to approximately 2.5, 5, 25 and 37.5 mg/kg/day. Four hours after the injection of radioactive iodine, uptake was decreased significantly in rats ingesting ETU at 500 or 750 ppm (25 or 37.5 mg/kg/day) for all feeding periods. At 24 hours after ^{131}I injection, uptake was significantly decreased in rats ingesting the 100-, 500- and 750-ppm doses for all feeding periods. Histologically, the thyroid glands of rats ingesting ETU at approximately 2.5 mg/kg, the NOAEL for this study, were not different from those of control rats. There was slight hyperplasia of the thyroid in rats given 100 ppm (5 mg/kg/day). At doses of 500 or 750 ppm (25 or 37.5 mg/kg/day), the thyroid had moderate to marked hyperplasia.

- The thyroid appears to be the primary target organ for ETU toxicity in longer-term exposure studies. Graham et al. (1973) measured ^{131}I uptake in male and female Charles River rats fed ETU (purity not specified) in the diet at 0, 5, 25, 125, 250 or 500 ppm for up to 12 months. Assuming that 1 ppm in the diet of older rats is equivalent to approximately 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0.25, 1.25, 6.25, 12.5 or 25 mg/kg/day. Adverse effects were noted at 2, 6 and 12 months. At 12 months, significant decreases in body weight and increases in thyroid weight were seen at the 125-, 250- and 500-ppm levels. Uptake of ^{131}I was significantly decreased in male rats after 12 months at 500 ppm, but was increased in females. Microscopic examination of the thyroid revealed the development of nodular hyperplasia at dose levels of 125 ppm and higher. The NOAEL for thyroid effects in this study was 25 ppm (approximately 1.25 mg/kg/day).

- Ulla [illegible]. (1972) reported a dose-related increased incidence of hyperplastic goiter in male and female rats fed ETU at 175 and 350 ppm in their diet for 18 months (approximately 8.75 and 17.5 mg/kg/day, based on Lehman, 1959). An increased incidence (significance not specified) of simple goiter was also reported in all treatment groups.

- In a 2-year study by Graham et al. (1975), Charles River rats were fed ETU (purity not specified) in the diet at 0, 5, 25, 125, 250 or 500 ppm (approximately 0.25, 1.25, 6.25, 12.5 or 25 mg/kg/day, based on Lehman, 1959). Statistically significant ($p < 0.01$) decreases in body weight were observed in both sexes fed at 500 ppm. Increases in thyroid-to-body weight ratios were apparent at 250 and 500 ppm ($p < 0.01$). There was an increased iodine (^{131}I) uptake at 5 ppm and a decreased uptake at 500 ppm, as well as slight thyroid hyperplasia at the 5- and 25-ppm dose levels (significance not stated). Based on these results, a LOAEL for lifetime exposure of 5 ppm (0.25 mg/kg/day) was identified.

Reproductive Effects

- Plasterer et al. (1985) administered ETU (purity not specified) by gavage as a water slurry to CD-1 mice at 600 mg/kg/day on days 7 to 14 of gestation. At this dose level, maternal toxicity was not observed but the reproductive index was significantly decreased ($p < 0.05$), indicating severe prenatal lethality.

- New Zealand White rabbits were dosed with ETU (100% pure) at 10, 20, 40 or 80 mg/kg/day on days 7 to 20 of pregnancy (Khera, 1973). Observed effects included an increase ($p < 0.05$) in resorption sites at 80 mg/kg. No adverse effects on fetal weight or on the number of viable fetuses per pregnancy were noted at any dose level, and no signs of maternal toxicity were observed. Based on the results of this study, a NOAEL of 80 mg/kg/day for maternal toxicity and a NOAEL of 40 mg/kg/day for fetotoxicity were identified.

Developmental Effects

- The ability of ETU to induce various adverse effects, including teratogenicity and maternal toxicity, has been demonstrated by several investigators using various animal models. Available data indicate that rats are probably the most sensitive species.

- Khera (1973) orally administered ETU (100% pure) to Wistar rats at daily doses of 5, 10, 20, 40 or 80 mg/kg from 21 or 42 days before conception to pregnancy day 15 and on days 6 to 15 or 7 to 20 of pregnancy. Dose-dependent lesions of the fetal central nervous and skeletal systems were produced, irrespective of the time at which ETU was administered. Teratogenic effects seen at the two highest dose levels included meningoencephalocele, meningorrhagia, meningorrhea, hydrocephalus, obliterated neural canal, abnormal pelvic limb posture with equinovarus, micrognathia, oligodactyly, and absent, short or kinky tail. Less serious defects were seen at 20 mg/kg, and at 10 mg/kg there was only a retardation of parietal ossification and of cerebellar Purkinje-cell migration. Retarded parietal ossification was the only abnormality seen at 5 mg/kg (significance not stated), its incidence being limited to small areas and to a few large litters. No signs of maternal toxicity were observed in rats administered ETU at 40 mg/kg/day for 57 days (42 days preconception to day 15 of gestation). Based on the results of this phase of the study, the

NOAEL for maternal toxicity was 40 mg/kg/day, and the NOAEL for developmental effects was 5 mg/kg/day.

- In the same study (Khera, 1973) New Zealand White rabbits were dosed with ETU at 10, 20, 40 or 80 mg/kg/day on days 7 to 20 of pregnancy. Observed effects included a reduction in fetal brain:body weight ratio at 10 and 80 mg/kg ($p < 0.01$). Renal lesions, characterized by degeneration of the proximal convoluted tubules, were noted microscopically (dose level not specified), but there were no skeletal abnormalities that were attributed by the authors to ETU. The results of this study are not useful for determining a NOAEL or LOAEL.

- Dose-related central nervous system (CNS) lesions in Wistar rat fetuses were reported by Khera and Tryphonas (1985). Ethylene thiourea (>98% pure) was administered by gastric intubation at 0, 15 or 30 mg/kg to dams on day 13 of pregnancy. Observed lesions at 30 mg/kg included histopathological changes of the CNS such as karyorrhexis in the germinal layer of basal lamina extending from the thoracic spinal cord to the telencephalon, and obliteration and duplication of the central canal and disorganization of the germinal and mantle layers. In the brain, the ventricular lining was fully denuded, neuroepithelial cells were arranged in the form of rosettes and nerve cell proliferation was disorganized. In the 15-mg/kg/day group, cellular necrosis was less severe and consisted of small groups of cells dispersed in the germinal layers of the neuraxis. None of the dams treated with ETU at any level in this study showed any overt signs of toxicity. Based on the results of this study, the NOAEL for maternal toxicity was 30 mg/kg and the LOAEL for developmental toxicity was 15 mg/kg.

- Sato et al. (1985) investigated the teratogenic effects of ETU (purity not specified) on Long-Evans rats exposed by gastric intubation to a single dose of 80, 120 or 160 mg/kg on one day between days 11 and 19 of gestation. Fetal malformations were related to both the day of administration and the dosage level. A short or absent tail was noted, for example, in 100% of fetuses exposed to ETU on gestational day 11 to 14. On day 11, a dose-dependent incidence of spina bifida and myeloschisis with hind-brain crowding were observed. A high incidence (48 to 87.5%, not dose-related) of macrocephaly with occipital bossing was noted, with administration of ETU on day 12, and an almost total incidence (96 to 100%) with administration on day 13. Other abnormalities seen in this study were exencephaly, microcephaly and hypognathia, and extremely high incidences (100% in many groups) of hydroencephaly and hydrocephalus, especially associated with administration days 14 through 19. Maternal toxicity was not addressed by the authors. The results of this study are not useful in determining LOAELs or NOAELs for teratogenicity or maternal toxicity, but serve instead as evidence of the kinds of developmental effects that a single dose of ETU at 80 mg/kg can induce teratogenic effects in rats.

- Khera and Iverson (1978) reported that there was no clear evidence of teratogenicity in kittens whose mothers had been administered ETU (purity not specified) at 5, 10, 30, 60 or 120 mg/kg by gelatin capsule for days 16 to 35 of gestation. However, fetuses from cats in a moribund state subsequent to ETU toxicosis (30 to 120 mg/kg dosage groups) did show a high incidence (11/35) of malformations including coloboma, umbilical hernia, spina bifida and cleft palate. Maternal toxicity and death were observed at dose levels of 10 mg/kg and above, manifesting signs of toxicity that were delayed in onset and characterized by progressive loss of body weight, ataxia, tremors and hind-limb paralysis. In this study, the NOAEL for maternal toxicity was identified as 5 mg/kg/day and the NOAEL for developmental effects was 10 mg/kg/day.

- Chernoff et al. (1979) demonstrated the teratogenic effects of ETU in Sprague-Dawley rats, CD-1 mice and golden hamsters. The rats were administered ETU (purity not specified) by gastric intubation at 80 mg/kg/day on days 7 to 21 of gestation. Gross defects of the skeletal system (micrognathia, micromelia, oligodactyly, kyphosis) and the CNS (hydrocephalus, encephalocele), as well as cleft palate were noted in a majority of fetuses at this dose level. No clear evidence of teratogenicity was seen in groups of rats administered dose levels of 5 to 40 mg/kg/day. No similar pattern of defects was observed in CD-1 mice dosed at 100 or 200 mg/kg/day on days 7 to 16 of gestation or in golden hamsters dosed at 75, 150 or 300 mg/kg/day on days 5 to 10 of gestation. Observations of maternal toxicity included a marked decrease in the average weight gain of pregnant rats dosed at 80 mg/kg/day ($p < 0.001$). No significant effects were observed in mice or hamsters. Based on the results of this study, the NOAELs for maternal and developmental toxicity were 40 mg/kg/day in the rat, 200 mg/kg/day in the mouse and 300 mg/kg/day in the hamster.

- Adverse developmental effects of orally administered ETU, including teratogenicity and/or maternal toxicity, have been reported at 60, 100 and 240 mg/kg in rats (Khera, 1982; Teramoto et al., 1975; Ruddick and Khera, 1975) and at 400 and 1,600 to 2,400 mg/kg in mice (Teramoto et al., 1980; Khera, 1984).

Mutagenicity

- Seiler (1973) described ETU as exhibiting weak but significant mutagenic activity in Salmonella typhimurium HIS G-46. A 2.5-fold increase in mutation frequencies ($p < 0.001$) was seen at intermediate concentrations (100 or 1,000 ppm/plate), but at higher concentrations (10,000 and 25,000 ppm) ETU was somewhat lethal to the test colonies resulting in lower relative mutagenic indices (1.60 and 1.16, respectively).

- Schupbach and Hummler (1977) reported that ETU induced mutations of the base-pair substitution type in S. typhimurium TA 1530 in vitro as well as in a host-mediated assay. In the host-mediated assay, a dose of 6,000 mg/kg (LD_{50} = 5,400 mg/kg) resulted in a slight but significant increase of the reversion frequency by a factor of 2.37. Results of a micronucleus test were negative after twofold oral administrations of 700, 1,850 or 6,000 mg/kg to Swiss albino mice; it was concluded that ETU does not induce any chromosomal anomalies in the bone marrow. No dominant-lethal effect was observed after single oral doses of 500, 1,000 or 3,500 mg/kg were given to male mice.

Carcinogenicity

- Graham et al. (1975) reported that ETU was a follicular thyroid carcinogen in male and female Charles River rats that were fed the compound (purity not specified) for 2 years at dietary levels of 250 and 500 ppm (approximately 12.5 and 25 mg/kg/day based on Lehman, 1959).

- In a survey of several compounds for tumorigenicity, Innes et al. (1969) reported that ETU (purity not stated) administered by diet to two strains of specific pathogen-free hybrid mice at a daily dosage of 215 mg/kg/day for 18 months resulted in statistically significant ($p < 0.01$) increases in hepatomas (14/16 or 18/18 for males and 18/18 or 9/16 for females) and in total tumor incidence. Pulmonary tumors and lymphomas were also investigated, but were not found to occur in the ETU group. The thyroid was not evaluated in this study. No other dose level was tested.

- Dose-related incidences of follicular and papillary thyroid cancers with pulmonary metastases and related lesions such as thyroid solid-cell adenomas were reported in Charles River CD rats by Ulland et al. (1972). Ethylene thiourea (97% pure) was administered by diet for 18 months at 175 or 350 ppm followed by administration of a control diet for 6 months. Assuming that 1 ppm in the diet of older rats is equivalent to approximately 0.05 mg/kg/day (Lehman, 1959) these levels correspond to doses of about 8.75 and 17.5 mg/kg/day. The first tumor was found after 68 weeks, and most were detected after 18 to 24 months when the study was terminated. The statistical significance of the reported findings was not addressed

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data located in the available literature were suitable for determination of the One-day HA value. It is therefore recommended that the Ten-day HA value for the 10-kg child (0.3 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-Day Health Advisory

The study by Freudenthal (1977) has been selected to serve as the basis for determination of the Ten-day HA for a 10-kg child. ETU was fed to a group of rats (20/sex group) for up to 90 days at levels of 0, 1, 5, 25, 125 or 625 ppm (0, 0.1, 0.5, 2.5, 12.5 or 62.5 mg/kg/day assuming that 1 ppm in the diet of a young rat equals 0.1 mg/kg/day, based on Lehman, 1959). Toxic effects on thyroid function and morphology were observed after 30 days' exposure to 125 ppm or greater. No adverse effects were noted in the 25-ppm group (2.5 mg/kg). Developmental effects reported in other studies have been reported in rats exposed in utero at 5 mg/kg (delayed parietal ossification) (Khera, 1973). The adversity of this effect is unclear. Khera and Iverson (1978) have reported maternal toxicity and death in cats exposed to 10 mg/kg. Therefore, 2.5 mg/kg was selected as a conservative NOAEL for deriving the Ten-day HA.

Using the NOAEL of 2.5 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(2.5\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.25\ \text{mg/L}\ (300\ \text{ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of fetal or maternal toxicity in rats exposed to ETU for 30 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The study [illegible]raham et al. (1973) has been selected to serve as the basis for determination of the Longer-term HA. In a 12-month study, ^{131}I uptake was measured in male and female Charles River rats fed ETU (purity not specified) in the diet at 5, 25, 125, 250 or 500 ppm for 2, 6 or 12 months.

Assuming that 1 ppm in the diet of older rats is equivalent to approximately 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0.25, 1.25, 6.25, 12.5 or 25 mg/kg/day.

Adverse effects were noted at all three test intervals. At 12 months, significant decreases in body weight and increases in thyroid weight were seen at the 125-, 250- and 500-ppm levels. Uptake of ^{131}I was significantly decreased in male rats after 12 months at 500 ppm but was increased in females. Microscopic examination of the thyroids revealed the development of nodular hyperplasia at dose levels of 125 ppm and higher. The NOAEL for thyroid effects in this study was 25 ppm (approximately 1.25 mg/kg/day).

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.25 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.125 \text{ mg/L } (100 \text{ ug/L})$$

where:

1.25 mg/kg/day = NOAEL, based on absence of thyroid effects in male rats exposed to ETU in the diet for up to 12 months.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed water consumption by a 10-kg child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{1.25 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.44 \text{ mg/L } (400 \text{ ug/L})$$

where:

1.25 mg/kg/day = NOAEL, based on absence of thyroid effects in male rats exposed to ETU in the diet for up to 12 months.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption by an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classifed as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986b), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Graham et al. (1975) was selected as the most appropriate basis for the calculation of a DWEL. In this 2-year study (presumably a continuation of the Graham et al. (1973) study, Charles River rats were fed ETU (purity not stated) in the diet at 5, 25, 125, 250 or 500 ppm (approximately 0.25, 1.25, 6.25, 12.5 or 25 mg/kg/day based on Lehman, 1959).

Statistically significant ($p < 0.01$) decreases in body weight were observed in both sexes fed at 500 ppm. Increases ($p < 0.01$) in thyroid-to-body weight ratios were apparent at 250 and 500 ppm. There was an increased iodine (^{131}I) uptake at 5 and 125 ppm and a decreased uptake at 500 ppm as well as slight thyroid hyperplasia at the 5- and 25-ppm dose levels (statistical significance not stated). This effect is considered to be biologically significant. Tumors were evident in animals in the 125-ppm group. Based on these results, the LOAEL for lifetime exposure was identified as 5 ppm (approximately 0.25 mg/kg/day).

Using the LOAEL of 0.25 mg/kg/day, the DWEL is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.25\ \text{mg/kg/day})}{(1,000)\ (10)} = 0.000025\ \text{mg/kg/day}\ (0.03\ \text{ug/kg/day})$$

where:

0.25 mg/kg/day = LOAEL, based on increased iodine intake as well as thyroid hyperplasia in rats exposed to ETU in the diet for 2 years.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

10 = additional uncertainty factor to account for the severity of effect and response at this dose level.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.00003\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 0.00105\ mg/L\ (1\ ug/L)$$

where:

0.00003 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

According to EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), ETU is classified in Group B: Probable human carcinogen. Therefore, a Lifetime Health Advisory is not recommended for ETU. The estimated cancer risk level associated with lifetime exposure to ETU at 1 ug/L is approximately 4.3×10^{-6}.

Evaluation of Carcinogenic Potential

- Three studies that evaluated the carcinogenic potential of ETU were identified. The results of these studies indicate that ETU is a thyroid carcinogen in rats (Graham et al., 1975; Ulland et al., 1972) and increases the incidence of hepatomas as well as total tumor incidence in mice (Innes et al., 1969).

- Graham et al. (1975) reported ETU to be a thyroid carcinogen in male and female Charles River rats that were fed the compound (purity not specified) for 2 years at dietary levels of 250 and 500 ppm (approximately 12.5 and 25 mg/kg/day in the diet of older rats based on Lehman, 1959). At 125 ppm (approximately 6.3 mg/kg/day), ETU was a thyroid oncogen.

- Dose-related incidences of follicular and papillary thyroid cancers with pulmonary metastases and related lesions such as thyroid solid-cell adenomas were reported in Charles River CD rats by Ulland et al. (1972). Ethylene thiourea (97% pure) was administered in the diet for 18 months at 175 and 350 ppm followed by administration of a control diet for 6 months. Assuming that 1 ppm in the diet of older rats is equivalent to approximately 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 8.75 and 17.5 mg/kg/day. The first tumor was found after 68 weeks, and most were detected after 18 to 24 months when the study was terminated. The statistical significance of the reported findings was not addressed.

- Innes et al. (1969) reported that ETU (purity not stated) administered by diet to specific pathogen-free hybrid mice at a daily dosage of 215 mg/kg/day for 18 months resulted in statistically significant ($p < 0.01$) increases in hepatomas and in total tumor incidence. No other dose level was tested. (Pulmonary tumors and lymphomas were also investigated in this study.)

- Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), ETU may be classified in Group B2: probable human carcinogen based on sufficient evidence from animal studies.

- The EPA Carcinogen Assessment Group estimated a one-hit slope of 0.1428/mg/kg/day based on the Innes et al. (1969) study identifying male mouse liver tumors as the sensitive sex/species end point (U.S. EPA, 1979). An assumed consumption of 2 liters of water per day by a 70-kg adult over a lifetime results in drinking water concentrations of 4, 2.4 and 0.24 ug/L for 10^{-4}, 10^{-5} and 10^{-6} cancer risk levels, respectively.

- Data are not available to estimate excess cancer risks using other mathematical models.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- No other data have been located for ETU.

VII. ANALYTICAL METHODS

- Ethylene thiourea is analyzed by a nitrogen-phosphorus detector/gas chromatographic method as described in Method #6 (U.S. EPA, 1988). In this procedure the ETU sample is mixed with ammonium chloride and potassium fluoride and passed through an exchange column (Extrelut). The ETU is then eluted with methylene chloride, concentrated for exchange with ethyl acetate to a volume of 5 mL. The method describes conditions which permit the separation and measurement of ETU by GC with a nitrogen-phosphorus detector. This method has been validated by a single laboratory. The estimated detection limit [illegible] ETU by Method #6 is 5 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No data were found on the removal of ethylene thiourea from drinking water by conventional treatment.

- No data were found on the removal of ethylene thiourea from drinking water by activated carbon adsorption. However, since ethylene thiourea has a high solubility and is hydrophilic, treatment with activated carbon probably would not be effective.

- No data were found on the removal of ethylene thiourea from drinking water by ion exchange. However, the structure of ethylene thiourea indicates it is not ionic and thus probably would not be amenable to ion exchange.

- No data were found on the removal of ethylene thiourea from drinking water by aeration. Since vapor pressure data are unavailable, Henry's

Coefficient, and thus the effectiveness of aeration, cannot be estimated. However, the high melting point and the high solubility indicate that Henry's Coefficient would be low and that aeration or air stripping probably would not be an effective form of treatment.

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August, 1988

FENAMIPHOS

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

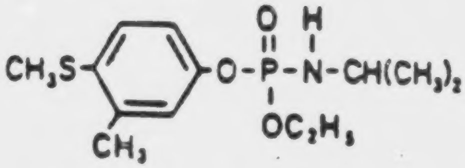
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 22224-92-6

Structural Formula



(1-Methylethyl)-ethyl-3-methyl-4-(methylthio)phenyl-phosphoramidate

Synonyms

- Nemacur; B 68138; Bay 68138; Bayer 68138; ENT 27572; Phenamiphos (Meister, 1983).

Uses

- Systemic nematicide (Meister, 1983).

Properties (Meister, 1983)

Chemical Formula	$C_{13}H_{22}O_3NSP$
Molecular Weight	303 (calculated)
Physical State (at 25°C)	Brown, waxy solid
Boiling Point	--
Melting Point	49.2°C
Density	--
Vapor Pressure (30°C)	7.5×10^{-7} mm Hg
Water Solubility (25°C)	400 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Fenamiphos has not been detected in 664 ground water samples analyzed from 659 locations (STORET, 1988). No surface water locations were tested.

Environmental Fate

- Ring-labeled ^{14}C-fenamiphos (radiochemical purity 94%), at 1 and 10 ppm, degraded with half-lives of 7 to 14 days in a buffered aqueous solution at pH 3 and >30 days at pH 9, and appeared to be stable at pH 7 when incubated in the dark at 30°C (McNamara and Wilson, 1981). In the pH 3 buffer solution, the primary degradation product was deaminated fenamiphos accounting for 74 to 78% of the applied material. Degradates identified in methylene chloride extracts from the pH 3, 7 and 9 solutions included fenamiphos sulfoxide, fenamiphos sulfone, fenamiphos phenol, fenamiphos sulfoxide phenol and fenamiphos sulfone phenol.

- Ring-labeled ^{14}C-fenamiphos (radiochemical purity >99%), at 12 ppm, degraded with a half-life of 2 to 4 hours in pH 7 buffered water irradiated with artificial light (approximately 5200 uW/cm^2, 300 to 600 nm) (Dime et al., 1983). After 24 hours of irradiation, fenamiphos accounted for approximately 4% of the applied radioactivity, fenamiphos sulfonic acid phenol for approximately 19%, fenamiphos sulfoxide for approximately 17%, fenamiphos sulfonic acid for approximately 6% (tentative identification), and fenamiphos sulfoxide phenol for approximately 1%. In the dark control, fenamiphos accounted for approximately 94% of the applied compound at 24 hours post-treatment.

- Ring-labeled ^{14}C-fenamiphos (radiochemical purity >99%), at approximately 20 ppm, degraded with a half-life of <1 hour on sandy loam soil irradiated with artificial light (approximately 6200 uW/cm^2, 300 to 600 nm) (Dime et al., 1983). After 48 hours of irradiation, fenamiphos and the degradates fenamiphos sulfoxide and fenamiphos sulfone accounted for approximately 12, 55 and 6% of the extractable radioactivity, respectively. In the dark control, fenamiphos accounted for approximately 93% of the extractable compound at 48 hours post-treatment.

- ^{14}C-Fenamiphos (purity 86%), at 3 ppm, degraded with a half-life of <4 days in silty clay loam soil previously treated with fenamiphos (Green et al., 1982). Fenamiphos sulfoxide comprised up to approximately 74% of the applied radioactivity (maximum at 11 days post-treatment); fenamiphos sulfone comprised approximately 10% and volatile ^{14}C-residues comprised 17% of the applied material at 55 days post-treatment. At 55 days post-treatment, 1.13% of the applied fenamiphos remained undegraded in the soil previously treated with fenamiphos, 5.41% remained undegraded in soil with no prior history of fenamiphos treatment, and 40.58% remained undegraded in sterile soil. Fenamiphos sulfoxide was the major degradate in all three treatments.

- ^{14}C-Fenamiphos (test substance uncharacterized), at 0.29 to 2.30 ug/mL of water, was adsorbed to sandy loam and clay loam soils with 26.3 to 30.0% and 42.2 to 52.3% of the applied radioactivity, respectively, adsorbed after 16 hours (Church, 1970).

- Fenamiphos (3 lb/gallon SC and 15% G), at approximately 20 lb ai/A, was mobile in columns (16-cm length) of sandy soil eluted with 10 inches of water. Fenamiphos was detected throughout the columns, and 0.9 to 2.2% of the applied material was recovered in the leachate (Gronberg and Atwell, 1980).

- Aged (30 days) ^{14}C-fenamiphos residues, at approximately 4 lb ai/A, were slightly mobile in a column (12-inch length) of sandy loam soil leached with 22.5 inches of water; approximately 2.3% of the applied radioactivity leached from the column and approximately 91% of the applied radioactivcity remained in the top 5 inches of the soil column (Tweedy and Houseworth, 1980).

III. PHARMACOKINETICS

Absorption

- Gronberg (1969) administered ^{14}C-labeled fenamiphos (99% purity) by oral intubation to rats. Only 5 to 7% was recovered in feces, indicating that 93 to 95% was absorbed from the gastrointestinal tract.

Distribution

- Gronberg (1969) administered single oral doses of 2 mg/kg of ethyl-^{14}C-fenamiphos (99% purity) by oral intubation to rats. Forty-eight hours after treatment, residues measured in tissues were: brain <0.1 ppm; heart 0.1 ppm; liver 0.8 to 1.7 ppm; kidney 0.4 to 0.5 ppm; fat 0.2 to 0.4 ppm; muscle <0.1 ppm; and gastrointestinal tract 0.2 ppm.

Metabolism

- In studies conducted by Gronberg (1969), rats were administered 2 mg/kg oral doses of fenamiphos (99% purity) using ethyl-^{14}C, methylthio-^{3}H or isopropyl-^{14}C label. The authors proposed a pathway of fenamiphos metabolism involving oxidation to the sulfoxide and sulfone analogs. Subsequent hydrolysis, conjugation and excretion via urine gave high molecular-weight compounds (600 to 800). No other details were provided.

Excretion

- Gronberg (1969) administered ethyl-^{14}C, methylthio-^{3}H or isopropyl-^{14}C-labeled fenamiphos (2 mg/kg, 99% purity) to rats by gavage. Thirty-nine to 42% or 50% of the administered radioactivity was expired as CO_2, respectively. Thirty-eight to 40% of the ethyl-^{14}C labels were in urine and 5% in feces, respectively. Eighty percent of the methylthio-^{3}H label was found in urine. The majority of the administered dose was excreted 12 to 15 hours after treatment.

IV. HEALTH EFFECTS

Humans

- No information on the health effects of fenamiphos in humans was found in the available literature, including any data on accidental poisoning (U.S. EPA, 1979).

Animals

Short-term Exposure

- NIOSH (1987) reported the acute oral LD_{50} of fenamiphos in the rat, mouse, dog, cat, rabbit and guinea pig as 8, 22.7, 10, 10, 10 and 75 mg/kg, respectively.

- Kimmerle and Lorke (1970) fed chickens (eight/dose) diets containing technical fenamiphos at levels of 0, 1, 3, 10 or 30 ppm active ingredient (a.i.) for 30 days. This corresponded to doses of 0, 2, 5, 16 or 26 mg/kg/day. Following treatment, feed consumption, neurotoxicity and cholinesterase (ChE) activity were determined. Histopathological sections of the brain, spinal cord and peripheral nerves were also evaluated. No neuropathy was observed at any dose level tested. No ChE symptoms were reported, but ChE activity in whole blood was inhibited in a dose-dependent manner from 21% at 3 ppm to 65% at 30 ppm. Based on ChE inhibition, a No-Observed-Adverse-Effect Level (NOAEL) of 1 ppm (2 mg/kg/day) was identified.

Dermal/Ocular Effects

- DuBois et al. (1967) reported acute dermal LD_{50} values of 78 mg/kg for rats.

- Crawford and Anderson (1973) applied 120 mg of a spray concentrate of fenamiphos (37.47% a.i.) to shaved intact and abraded skin of six New Zealand White rabbits and reported slight erythema 24 and 72 hours post-treatment.

- In ocular studies conducted by Crawford and Anderson (1973), the instillation of 0.1 mL of a spray concentrate of fenamiphos (37.47% a.i.) into the eyes of New Zealand White rabbits resulted in corneal and conjunctival damage at 24 and 72 hours post-treatment. These effects had not subsided by 21 days post-treatment.

Long-term Exposure

- In feeding studies conducted by Mobay Chemical Corporation (1983), Fischer 344 rats (50/sex/dose) were administered technical fenamiphos (89% purity) at dose levels of 0, 0.36, 0.60 or 1.0 ppm a.i. for 90 days. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to dose levels of 0, 0.018, 0.03 or 0.05 mg/kg/day. Following treatment, brain, plasma and erythrocyte ChE levels were measured. Cholinesterase levels were not significantly reduced at any dose tested. Other parameters were not evaluated. The author reported a NOAEL of 1 ppm (0.05 mg/kg/day, the highest dose tested).

- Loser and Kimmerle (1968) fed Wistar rats (15/sex/dose) fenamiphos (82% a.i.) for 90 days in the diet at dose levels of 0, 4, 8, 16 or 32 ppm active ingredient. Assuming that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.2, 0.4, 0.8 or 1.6 mg/kg/day. Following treatment, body weight, food consumption, hematology, ChE activity, urinalysis and gross pathology were evaluated. No histologic examination was performed. No effects on any end point were reported except for ChE inhibition. No effect was seen at 4 ppm (0.2 mg/kg/day). At 8 ppm (0.4 mg/kg/day), ChE in whole blood and plasma was decreased by 11% and 19%, respectively. Higher doses produced larger decreases in ChE. Based on these data, a NOAEL of 4 ppm (0.2 mg/kg/day) was identified.

- Loser (1970) administered technical fenamiphos (99.4% purity) in the feed of beagle dogs (two/sex/dose) for 3 months at dietary levels of 0, 1, 2 or 5 ppm. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.025, 0.05 or 0.125 mg/kg/day. Untreated controls (three/sex) were run concurrently. Following treatment, body weight, feed consumption, clinical chemistry, urinalysis, ChE activity and gross pathology were evaluated. At 5 ppm, there was a slight decrease in weight gain, although the author did not consider this to be important. No compound-related effects were reported in any other parameters measured except ChE activity. At 1 ppm, plasma ChE was inhibited 13% and 18%, and red blood cell ChE was inhibited 6% and 19% in males and females, respectively. At 2 ppm, plasma and red blood cell ChE was comparable to control levels in males, and was inhibited 13% in plasma and 16% in red blood cells in females. At 5 ppm, ChE in plasma was inhibited 44% and 41%,and red blood cell ChE was inhibited 26% and 22% (females and males, respectively). No brain ChE measurements were reported. Based on the absence of significant (>20%) ChE inhibition at 1 or 2 ppm, a NOAEL of 2 ppm (0.05 mg/kg/day) is identified.

- Hayes et al. (1982) administered fenamiphos (90% purity) in the diet to CD albino mice (50/sex/dose) at dose levels of 0, 2, 10 or 50 ppm for 20 months. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.3, 1.5 or 7.5 mg/kg/day. Following treatment, body weight, food consumption, hematology and mortality were evaluated. Absolute brain weights were decreased at 2 ppm (0.3 mg/kg/day) or greater. At 50 ppm (7.5 mg/kg/day), there was a decrease in body weight. Based on these data, a Lowest-Observed-Adverse-Effect Level (LOAEL) of 2 ppm (0.3 mg/kg/day), lowest dose tested, was identified, but not a NOAEL.

- Loser (1972a) administered technical fenamiphos (78.8% purity) in the diet of Wistar rats (40/sex/dose) for 2 years at dose levels of 0, 3, 10 or 30 ppm a.i. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.15, 0.5 or 1.5 mg/kg/day. Untreated controls (50 males, 60 females) were run concurrently. Following treatment, body weight, food consumption, hematology, urinalysis, plasma and erythrocyte ChE activity, gross pathology and histopathology were evaluated. At the highest dose (30 ppm), a slight increase in female mortality (38% versus 29% in controls) was noted, but the author did not consider this significant. There were statistically significant ($p < 0.05$) increases in thyroid gland and lung weights in females and in heart weight in males. No compound-related effects were observed in any of the other parameters measured except an inactivation of plasma and erythrocyte ChE. At 10 ppm, ChE was decreased by 18 to 41%, and at 30 ppm, ChE was decreased by 28 to 60%. No brain ChE measurements were reported. Based on ChE inhibition, the author identified a NOAEL of 3 ppm (0.15 mg/kg/day). Based on organ weight changes, the NOAEL was 10 ppm (0.5 mg/kg/day).

- In chronic feeding studies by Loser (1972b), beagle dogs (four/sex/dose) were administered technical fenamiphos (78.8% purity) in the feed for 2 years at 0, 0.5, 1, 2, 5 or 10 ppm active ingredient. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.013, 0.025, 0.050, 0.125 or 0.250 mg/kg/day. Following treatment, no compound-related effects were observed on appearance, general behavior, food consumption, clinical chemistry, hematology, gross pathology or histopathology at any dose tested. Plasma and erythrocyte ChE levels were inhibited about 26% at 2 ppm, about 21 to 57% at 5 ppm and about 32 to 51% at 10 ppm. Cholinesterase was not inhibited at 1 ppm (0.025 mg/kg/day) or below. Based on ChE inhibition, this study identified a NOAEL of 1 ppm (0.025 mg/kg/day) and a LOAEL of 2 ppm (0.05 mg/kg/day).

Reproductive Effects

- In a three-generation study conducted by Loser (1972c), FB30 rats (10 males or 20 females/dose) were fed technical fenamiphos (78.8%) in the diet at dose levels of 0, 3, 10 or 30 ppm active ingredient. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.15, 0.5 or 1.5 mg/kg/day. Fertility, lactation performance, pup development and parental and litter body weights were evaluated. No compound-related effects were observed in any parameter in animals exposed to 10 ppm (0.5 mg/kg/day) or less. At 30 ppm (1.5 mg/kg/day), one male of the F_{2b} generation showed a lower body weight gain than the untreated controls, but there were no differences in body weight gain in any other generation. Based on these data, a reproductive NOAEL of 30 ppm (1.5 mg/kg/day) was identified.

Developmental Effects

- MacKenzie et al. (1982) administered fenamiphos (88% a.i. by gavage to pregnant New Zealand White rabbits (20/dose) at dose levels of 0, 0.1, 0.3 or 1.0 mg/kg/day on days 6 to 18 of gestation. Following treatment, there was a decrease in maternal body weight at 0.3 mg/kg/day or above. At the 1.0-mg/kg/day level, eight dead pups and seven late resorptions were reported, and fetal weight was depressed. A significant ($p < 0.05$) increase in the incidence of chain-fused sternebrae was also observed at 1.0 mg/kg. Based on maternal body weight, a NOAEL of 0.1 mg/kg was identified. Based on fetotoxicity and teratogenicity, a NOAEL of 0.3 mg/kg/day was identified.

Mutagenicity

- Herbold (1979) reported that fenamiphos was not mutagenic in Salmonella typhimurium (TA 1535, 1537, 98 or 100) up to 2,500 ug/plate, either with or without activation.
- In a dominant lethal test with male NMRI mice (Herbold and Lorke, 1980), acute oral doses of 5 mg/kg did not produce mutagenic effects.

Carcinogenicity

- Hayes et al. (1982) administered fenamiphos (90% purity) for 20 months in the diet to CD albino mice (50/sex/dose) at dose levels of 0, 2, 10 or 50 ppm (0, 0.3, 1.5 or 7.5 mg/kg/day). Based on gross and histopathologic examination, neoplasms in various tissues and organs were similar in type, organization, time of occurrence and incidence in control and treated animals.
- Loser (1972a) administered technical fenamiphos (78.8% purity) in the diet of Wistar rats (40/sex/dose) for 2 years at dose levels of 3, 10 or 30 ppm active ingredient. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0.15, 0.5 or 1.5 mg/kg/day. Untreated controls (50 males, 60 females) were run concurrently. No evidence of carcinogenicity was detected either by gross or histological examination.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption by a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for fenamiphos. It is therefore recommended that the Ten-day HA value for the 10-kg child of 0.009 mg/L (9 ug/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by MacKenzie et al. (1982) has been selected to serve as the basis for determination the Ten-day HA value for fenamiphos. In this study, pregnant rabbits (20/dose) were administered technical fenamiphos (88% purity) by gavage at dose levels of 0, 0.1, 0.3 or 1.0 mg/kg on days 6 through 18 of gestation. A decrease in maternal body weight was observed in animals dosed with 0.3 mg/kg/day or above. No maternal toxicity was reported at 0.1 mg/kg/day. No fetotoxicity or teratogenic effects were observed at 1.0 mg/kg or less or 0.3 mg/kg or less, respectively. Chain fusion of sternebrae were observed in the 1.0 mg/kg group. Based on maternal effects, a NOAEL of 0.1 mg/kg/day was identified.

Using a NOAEL of 0.1 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.1\ \text{mg/kg/day})\ (10\ \text{kg})\ (0.88)}{(100)\ (1\ \text{L/day})} = 0.009\ \text{mg/L}\ (9\ \text{ug/L})$$

where:

0.1 mg/kg/day = NOAEL, based on absence of maternal or fetal toxicity in rabbits exposed to fenamiphos via gavage on days 6 through 18 of gestation.

10 kg = assumed body weight of a child.

0.88 = correction factor to account for 88% active ingredient in administered doses.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed water consumption of a child.

Longer-term Health Advisory

The study by Loser (1970) has been selected to serve as the basis for determination of the Longer-term HA value for fenamiphos. In this study, beagle dogs (two/sex/dose) were fed technical fenamiphos (99.4% purity) in the diet at dose levels of 0, 1, 2 or 5 ppm (0, 0.025, 0.05 or 0.125 mg/kg/day) for 3 months. No effects were detected on body weight, food consumption, clinical chemistry, urinalysis and gross pathology. The only effect observed was inhibition of plasma and erythrocyte ChE activity at the 5 ppm dose level (0.125 mg/kg/day). No significant effect was seen at 2 ppm or less (0.05 mg/kg/day), which was identified as the NOAEL. The 90-day study in F344 rats by Mobay Chemical Corporation (1983) identified a NOAEL of 1 ppm (0.05 mg/kg/day), but this was not considered, since it was the highest dose tested and a LOAEL was not identified. The study by Loser and Kimmerle (1968) identified a NOAEL of 0.2 mg/kg/day in rats, but this was not chosen, since available data (Loser et al., 1972a,b) suggest that the rat is less sensitive than the beagle dog.

Using a NOAEL of 0.05 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.05\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.005\ \text{mg/L}\ (5\ \text{ug/L})$$

where:

0.05 mg/kg/day = NOAEL, based on absence of significant cholinesterase inhibition in dogs exposed to fenamiphos via the diet for 3 months.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption by a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.05\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 0.018\ \text{mg/L}\ (20\ \text{ug/L})$$

where:

0.05 mg/kg/day = NOAEL, based on absence of significant cholinesterase inhibition in dogs exposed to fenamiphos via the diet for 3 months.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor. From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Loser (1972b) has been selected to serve as the basis for determination of the Lifetime HA value for fenamiphos. In this study, dogs (four/sex/dose) were fed technical fenamiphos (78.8% purity) in the diet for 2 years at dose levels of 0, 0.5, 1, 2, 5 or 10 ppm active ingredient (0, 0.013, 0.025, 0.05, 0.125 or 0.25 mg/kg/day). The only effect detected was inhibition of plasma and erythrocyte cholinesterase at dose levels of 2, 5 or 10 ppm (0.05, 0.125 or 0.25 mg/kg/day). The NOAEL identified in this study was 1 ppm (0.025 mg/kg/day). The chronic studies in rats by Loser (1972a) and by Hayes et al. (1982) were not chosen, since the data indicate the rat is less sensitive than the dog.

Using a NOAEL of 0.025 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.025\ \text{mg/kg/day})}{(100)} = 0.00025\ \text{mg/kg/day}$$

where:

0.025 mg/kg/day = NOAEL, based on absence of cholinesterase inhibition in dogs exposed to technical fenamiphos via the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{0.00025\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.009\ \text{mg/day}\ (9\ \text{ug/L})$$

where:

0.00025 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.009\ \text{mg/L})\ (20\%) = 0.0018\ \text{mg/L}\ (2\ \text{ug/L})$$

where:

0.009 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenic potential was detected in chronic feeding studies in rats (Loser, 1972a) or mice (Hayes et al., 1982).
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of fenamiphos.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), fenamiphos may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Residue tolerances have been established for fenamiphos and its cholinesterase-inhibiting metabolites in or on various agricultural commodities at 0.02 to 0.60 ppm based on an ADI for fenamiphos of 0.0025 mg/kg/day (U.S. EPA, 1985).
- The World Health Organization (WHO) calculated a TADI of 0.0003 mg/kg/day for fenamiphos (Vettorazzi and Van den Hurk, 1985).

VII. ANALYTICAL METHODS

- Analysis of fenamiphos is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus-containing pesticides in water samples (Method #507, U.S. EPA, 1988).

In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen-phosphorus detector. The method has been validated in a single laboratory. The estimated detection limits for analytes with this method, including fenamiphos, is 1.0 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information was found in the available literature on treatment technologies used to remove fenamiphos from contaminated water.

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*Confidential Business Information submitted to the Office of Pesticide Programs

August, 1988

FLUOMETURON

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

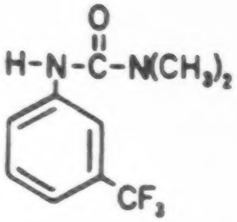
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 2164-17-2

Structural Formula



N,N-Dimethyl-N-(3-(trifluoromethyl)phenyl)-urea

Synonyms

- C 2059; Cotoron; Cottonex; (Meister, 1988).

Uses

- Preemergence and postemergence control of annual grasses and broadleaves in cotton and sugarcane (Meister, 1988).

Properties (Windholz et al., 1983; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_{10}H_{11}ON_2F_3$
Molecular Weight	232.21
Physical State (25°C)	White crystals
Boiling Point	--
Melting Point	163-164.5°C
Density	--
Vapor Pressure (20°C)	5×10^{-7} mm Hg
Specific Gravity	--
Water Solubility (25°C)	80 mg/L
Octanol/Water Partition Coefficient	1.88 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Fluometuron was not found in any of 156 ground water samples analyzed from 125 locations or in 14 surface water samples analyzed from 14 locations (STORET, 1988). This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- ^{14}C-Fluometuron (test substance not characterized) was intermediately mobile (R_f = 0.50) in a silty clay loam soil (2.5% organic matter) based on thin-layer chromatography (TLC) tests of soil (Helling, 1971; Helling et al., 1971).

- ^{14}C-Fluometuron (test substance not characterized), at various concentrations, was very mobile in a Norge loam soil (1.7% organic matter) with a Freundlich-K of 0.31 (Davidson and McDougal, 1973). Freundlich-K values, determined in soil:water slurries (5-10 g/100 mL) treated with ^{14}C-fluometuron (test substance not characterized) at 0.05 to 10.0 ppm, were 0.37 for Uvrier sand (1% organic matter), 1.07 for Collombey sand (2.2% organic matter), 1.66 for Les Evouettes loam (3.6% organic matter), 3.16 for Vetroz sandy clay loam (5.6% organic matter), and 1.36 for Illarsatz high organic soil (22.9% organic matter) (Guth, 1972).

- Fruendlich-K values were positively correlated with the organic matter content of the soil. Fluometuron (test substance not characterized), at 10 to 80 uM/kg, was adsorbed at 10 to 51% of the applied amount to a loamy sand soil (1.15% organic matter) and 16 to 67% of the applied to a sandy loam soil (1.9% organic matter) in water slurries during a test period of 1 minute to 7 days, with adsorption increasing with time (LaFleur, 1979). Approximately 22% of the applied fluometuron desorbed in water from the loamy sand soil and 15% desorbed from the sandy loam soil during a 7-day test period.

- Fluometuron (50% wettable powder, WP) dissipated from the 0- to 5-cm depth of a sandy clay loam soil (3.2% organic matter) in central Europe with a half-life of less than 30 days (Guth et al., 1969). Fluometuron residues (not characterized) dissipated with a half-life of 30 to 90 days.

III. PHARMACOKINETICS

Absorption

- Boyd and Fogleman (1967) reported that fluometuron is slowly absorbed from the gastrointestinal (GI) tract of female CFE rats (200 to 250 g). Based on the radioactivity recovered in the urine and feces of four rats given 50 mg ^{14}C-labeled fluometuron after a 2-week pretreatment with 1,000 ppm unlabeled fluometuron (estimated as 100 mg/kg/day, assuming 1 ppm equals 0.1 mg/kg/day in the young rat [Lehman, 1959]), the test compound appears not to have been fully absorbed within 72 hours. Of an orally administered dose (50 mg/kg), up to 15% was excreted in the urine and 49% in the feces.

Distribution

- Boyd and Fogleman (1967) detected radioactivity in the liver, kidneys, adrenals, pituitary, red blood cells, blood plasma and spleen 72 hours after oral administration of ^{14}C-labeled fluometuron at dose levels of

50 or 500 mg/kg in rats. The highest concentration was detected in red blood cells.

Metabolism

- Boyd and Fogleman (1967) concluded that, by thin-layer chromatographic analysis, the urine of rats in their study contained m-trifluoromethylaniline, desmethyl-fluometuron, demethylated fluometuron, hydroxylated desmethyl-fluometuron, hydroxylated demethylated fluometuron, and hydroxylated aniline.
- Lin et al. (1976) reported that after incubation of $^{14}CF_3$-labeled fluometuron with cultured human embryonic lung cells for up to 72 hours, 95% of the compound remained unchanged. Human embryonic lung cell homogenate metabolized small amounts of fluometuron through oxidative pathways to N-(3-trifluoromethylphenyl)-N-formyl-N-methylurea, N-(3-trifluoromethylphenyl)-N-methylurea, and N-(3-trifluoromethylphenyl) urea.

Excretion

- Boyd and Fogleman (1967) reported that urinary excretion of radioactive label peaked at 24 hours after administration of ^{14}C-fluometuron (50 mg/kg) and decreased during the remaining 48 hours. Seventy-two hours after oral administration of the radioactive label, up to 15% of the administered dose was eliminated in the urine.
- In the study by Boyd and Fogleman (1967), fecal excretion of fluometuron peaked by 48 hours postdosing and decreased over the remaining 24 hours. Forty-nine percent of the administered dose (50 mg/kg) was eliminated in the feces.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of fluometuron in humans.

Animals

Short-term Exposure

- NIOSH (1985) reported the acute oral LD_{50} values of fluometuron as 6,416, 2,500, 900 and 810 mg/kg in the rat, rabbit, mouse and guinea pig, respectively.
- Sachsse and Bathe (1975) reported an acute oral LD_{50} value of 4,636 mg/kg for both male and female Tif RA1 rats.
- Foglemann (1964a) reported the acute oral LD_{50} values for CFW albino mice as 2,300 mg/kg in females and 900 mg/kg in males.

Dermal/Ocular Effects

- Siglin et al. (1981) conducted a primary dermal irritation study in which undiluted fluometuron powder (80%) was applied to intact and abraded skin of six young adult New Zealand White rabbits for 24 hours. The test substance was severely irritating, with eschar formation observed at 24 and 72 hours.

- Fogleman (1964b) exposed the skin of eight albino rabbits (four/sex) to a 10% aqueous suspension of fluometuron (applied under rubber dental damming) for 6 hours/day for 10 days. No contact sensitization developed during the exposure period. Weight depression at day 130 was evident in the treated group.

- Galloway (1984) reported no sensitizing reactions in Hartley albino guinea pigs exposed to undiluted fluometuron on alternate days for 22 days and on day 36.

- Technical fluometuron was not found to be an eye irritant in rabbits (Fogleman, 1964c).

Long-term Exposure

- Fogleman (1965a) conducted a 90-day feeding study in which CFE rats (15/sex/dose) were administered technical fluometuron (purity not specified) in the diet at dose levels of 100, 1,000 or 10,000 ppm (reported as 7.5, 75 or 750 mg/kg/day). Following exposure, various parameters including hematology, clinical chemistry and histopathology were evaluated. Enlarged, darkened spleens were observed grossly in male rats given 75 mg/kg/day. At the highest dose level, a depression in body weight and congestion in the parenchyma of the spleen, adrenals, liver and kidneys were evident. A mild deposition of hemosiderin in the spleen was also evident. Spleens were large and dark; livers were brownish and muddy colored; and kidneys were small with discolored pelvises in high-dose males. Histopathological findings were confined to mild congestion in various organs and mild hemosiderin deposits in the spleens of high-dose rats. No effects were evident in rats given the 7.5 mg/kg/day dose level for any parameter measured. This dose level was identified as the No-Observed-Adverse-Effect Level (NOAEL) for this study.

- Fogleman (1965b) administered technical fluometuron (purity not stated) in feed to three groups of beagle pups (three/sex/dose) at dose levels of 40, 400 or 4,000 ppm (reported as 1.5, 15 or 150 mg/kg/day) for 90 days. At 150 mg/kg/day, mild inflammatory-type reactions and congestion in the liver and kidneys and mild congestion and hemosiderin deposits in the spleen were observed. Also at this high dose, the spleen to body weight ratio was slightly increased. No adverse systemic effects were observed in dogs administered 1.5 or 15 mg/kg/day (NOAEL).

- In the NCI (1980) study, $B6C3F_1$ mice and F344 rats (10 of each sex) were given fluometuron (>99% pure) in the diet for 90 days at 250, 500, 1,000, 2,000, 4,000, 8,000, and 16,000 ppm. Decreased body weight gain (>10%) was apparent with doses above 2,000 ppm. Treatment-related splenomegaly was found in rats with doses above 1,000 ppm. Microscopic examination was done on spleens only from rats given more than 2,000 ppm, and this assessment indicated dose-related changes including hyperemia of red pulp with atrophy of Malpighian corpuscles and depletion of lymphocytic elements. Body weight gain was reduced (>10%) in male and female mice given more than 2,000 ppm. Assuming that 1 ppm in the diet equals 0.05 mg/kg/day in the rat and 0.15 mg/kg/day in the mouse (Lehman, 1959), 1,000 ppm (NOAEL) corresponds to 50 mg/kg/day in rats and 2,000 ppm (NOAEL) corresponds to 300 mg/kg/day in mice.

- Hofmann (1966) administered 0, 3, 10, 30 or 100 mg/kg technical fluometuron (Cotoron = C-2059, purity not specified) as a suspension in 1% Mulgafarin six times per week for 1 year by pharnyx probe to four groups of Wistar rats (25/sex/dose). Following treatment, general behavior, mortality, growth, food consumption, clinical chemistry, blood, urine, and histopathology were evaluated. Males dosed with 30 or 100 mg/kg/day and females dosed with 100 mg/kg/day showed significant ($p < 0.05$) reductions in body weight at the end of the study compared to controls. No toxicological effects were observed in rats administered 3 or 10 mg/kg/day (NOAEL).

- In the NCI (1980) study, F344 rats (10 of each sex) were given fluometuron (>99% pure) at dietary levels of 250, 500, 1,000, 2,000 and 4,000 ppm in a repeat of the 90-day study to examine splenic effects more closely. Splenomegaly in all treated groups was noted. A dose-related increase in spleen weights and a dose-related decrease in circulating red blood cells were observed in females fed 250 ppm and higher. Increased spleen weights were evident in males given doses above 500 ppm. However, statistical analysis of the data was not done. Stated in the report without presentation of data is the observation of a dose-related increase in red blood cells with polychromasia and anisocytosis in male and female rats and congestion of red pulp with corresponding decrease of white pulp in spleen. Assuming that 1 ppm equals 0.05 mg/kg/day in the rat (Lehman, 1959), a Lowest-Observed-Adverse-Effect Level (LOAEL) of 250 ppm (12.5 mg/kg/day) is suggested in this study.

- No noncarcinogenic effects (survival, body weight and pathological changes) in $B6C3F_1$ mice and F344 rats were found in the NCI (1980) bioassay discussed under Carcinogenicity.

Reproductive Effects

- No information was found in the available literature on the effects of fluometuron on reproduction.

- A reproduction study with technical fluometuron in rats is in progress to satisfy U.S. EPA Office of Pesticide Programs (OPP) data requirements.

Developmental Effects

- Fritz (1971) reported a teratology study in rats in which dams were given C-2059 suspension in carboxymethylcellulose during days 6 through 15 of gestation. Offspring were removed on day 20 of gestation for examination. The NOAEL was indicated as 100 mg/kg/day, and higher doses reduced fetal body weight. However, this study was invalidated by the U.S. EPA OPP because of inadequate reporting.

- A teratology study in which pregnant Spf New Zealand rabbits were given technical fluometuron (purity not specified) by gavage at dose levels of 50, 500, and 1,000 mg/kg/day during gestation days 6 through 19 was reported by Arhur and Triana (1984). Does were examined for body weight, food consumption and pathological and developmental effects, and laparohysterectomy was done on gestation day 29 for pathological evaluation of fetuses. Increased liver weights and increased mean number of resorptions were found with all doses ($p < 0.05$ at the low and mid doses; insufficient number of fetuses for statistical analysis at the high dose). A LOAEL of 50 mg/kg/day was identified. Reductions in body weights and food consumption occurred in does given 500 and 1,000 mg/kg/day. Deaths, abortions and perforated stomachs were observed in does given 1,000 mg/kg/day.

Mutagenicity

- In bacterial assays (Dunkel and Simmon, 1980), fluometuron (6.6 mg/plate) was not mutagenic in Salmonella strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100, either with or without metabolic activation.

- Seiler (1978) reported that fluometuron (2,000 mg/kg bw) given as a single oral dose of an aqueous suspension by gavage resulted in a strong inhibition of mouse testicular DNA synthesis in mice killed 3.5 hours after treatment. Results were inconclusive in a subsequent micronucleus test.

- In yeast assays (Seibert and Lemperle, 1974), a commercial formulation of fluometuron was ineffective in inducing mitotic gene conversion in Saccharomyces cerevisiae strain D4 without exogenous metabolic activation.

Carcinogenicity

- In a long-term bioassay (NCI, 1980), fluometuron was administered in feed to F344 rats and B6C3F$_1$ mice. Groups of rats (50/sex/dose) were fed diets containing 125 or 250 ppm fluometuron for 103 weeks. Mice (50/sex/dose) were fed 500 or 1,000 ppm for an equivalent period of time. Assuming that 1 ppm equals 0.05 mg/kg/day in the older rat and 0.15 mg/kg/day in the mouse (Lehman, 1959), 125 and 250 ppm equaled 6.25 and 12.5 mg/kg/day in rats and 500 and 1,000 ppm equaled 75 and 150 mg/kg/day in mice. Results based on survival, body weights, and nonneoplastic pathology (including spleen) were negative in rats. Following treatment, there were no significant increases in tumor incidences in male or female F344 rats or in female B6C3F$_1$ mice compared to controls. In male B6C3F$_1$ mice, an increased incidence of hepatocellular carcinomas and adenomas was noted. The incidences were dose-related and were marginally higher than those in the corresponding matched controls or pooled controls from concurrent studies [matched control, 4/21 or 19%; low dose, 13/47 or 28%; high dose, 21/49 or 43% ($p = 0.049$); pooled controls, 44/167 or 26%]. NCI (1980) concluded that additional testing was needed because of equivocal findings for male mice and because both rats and mice may have been able to tolerate higher doses. The NOAELs identified for rats and mice are 12.5 and 75 mg/kg/day, respectively.

- Chronic feeding studies with technical fluometuron in rats and mice are ongoing to satisfy OPP data requirements.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000) in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for fluometuron. The teratology study by Arhur and Triana (1984) was not selected because a NOAEL was not identified. It is therefore recommended that the Longer-term HA value for a 10-kg child (2 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

No information was found in the available literature that was suitable for determination of the Ten-day HA value for fluometuron. The teratology study by Arhur and Triana (1984) was not selected because a NOAEL was not identified. It is therefore recommended that the Longer-term HA value for a

10-kg child (2 mg/L, calculated below) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The 90-day feeding study in dogs by Fogleman (1965b) has been selected to serve as the basis for the Longer-term HA value for fluometuron. In this study, dogs given technical fluometuron at dose levels of 0, 1.5, 15 or 150 mg/kg/day in the diet for 90 days showed pathological effects in spleen, liver and kidney at the highest dose and no observable effects at the lower doses. The 90-day feeding studies with rats by Fogleman (1965a) and NCI (1980) were not selected because the 15 mg/kg/day NOAEL in the Fogleman (1965b) study was below the lowest dose of 75 mg/kg/day in the Fogleman (1965a) study where effects were noted, and pathological changes in spleen found with the dietary level of 12.5 mg/kg/day in the repeat NCI (1980) 90-day study in rats were not found with this level in the initial 90-day study and in the 2-year bioassay in rats by the NCI (1980). Because 7.5 mg/kg/day in the Fogleman (1965a) study and 12.5 mg/kg/day (estimated) in the NCI (1980) carcinogenicity bioassay were NOAELs, it is concluded that 15 mg/kg/day would be consistent with a NOAEL in these 90-day studies in rats. The study by Hofmann (1966) in which rats were given technical fluometuron as a suspension by gavage at dose levels of 0, 3, 10, 30 and 100 mg/kg, six times per week for 1 year, was not selected because feeding the substance in the diet is preferred over giving it as a suspension by gavage for estimating exposure from drinking water, although the 10 mg/kg NOAEL in this study approximates the 15 mg/kg/day NOAEL in the Fogleman (1965b) study. The 90-day feeding study in mice by NCI (1980) was not selected because the NOAEL of 300 mg/kg/day (estimated) is above the effect levels in the other studies considered. The 15 mg/kg/day dose level in dogs was, therefore, identified as the NOAEL.

Using a NOAEL of 15 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(15\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 1.5\ \text{mg/L}\ (2{,}000\ \text{ug/L})$$

where:

15 mg/kg/day = NOAEL, based on absence of pathological changes in the spleen, liver and kidneys of dogs exposed to the test substance in the diet for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(15\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 5.3\ \text{mg/L}\ (5{,}000\ \text{ug/L})$$

where:

15 mg/kg/day = NOAEL, based on absence of pathological changes in the spleen, liver and kidneys of dogs exposed to the test substance in the diet for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The NCI (1980) carcinogenicity bioassay in F344 rats has been selected to serve as the basis for determination of the Lifetime HA value for fluometuron. Rats were exposed to dose levels of 0, 125 and 250 ppm fluometuron in the diet (estimated as 6.25 and 12.5 mg/kg/day) for 103 weeks. No observable effects were evident in this study. Although pathological changes in spleens of rats given 250 ppm fluometuron in the diet (estimated as 12.5 mg/kg/day) were noted in the repeat 90-day study in rats by NCI (1980), it appears that splenic lesions were either not evident or were able to reverse in the rats given the 250-ppm dietary level for 2 years (only one rat died by 1 year into the bioassay). Furthermore, pathological changes in the spleen were not evident with doses below 2,000 ppm in the initial 90-day study in F344 rats by NCI (1980). The 90-day and 1-year studies discussed under Longer-term Health Advisory have not been selected for calculation of a Lifetime HA because of their short duration compared to the 103-week NCI (1980) bioassay and because, although not as many end points were assessed in the NCI (1980) bioassay compared to these studies, major effects observed in these studies (pathology, body weight) were evaluated in the NCI (1980) bioassay. The NCI (1980) bioassay in B6C3F$_1$ mice was not considered because higher dose levels (500 and 1,000 ppm, estimated as 75 and 150 mg/kg/day) were used.

Using the NCI (1980) bioassay in rats with a NOAEL of 12.5 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(12.5\ \text{mg/kg/day})}{(100)(10)} = 0.0125\ \text{mg/kg/day}\ \text{(rounded to 0.013 mg/kg/day)}$$

where:

12.5 mg/kg/day = NOAEL, based on absence of observable effects in rats exposed to fluometuron in the diet for 103 weeks.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

10 = additional uncertainty factor used by U.S. EPA OPP to account for data gaps (chronic feeding studies in rats and dogs, reproduction study in rats, teratology studies in rats and rabbits).

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.013\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.455\ \text{mg/L}\ (500\ \text{ug/L})$$

where:

0.013 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.46\ \text{mg/L})\ (20\%) = 0.09\ \text{mg/L}\ (90\ \text{ug/L})$$

where:

0.46 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- NCI (1980) determined that fluometuron was not carcinogenic in male and female F344 rats and female mice ($B6C3F_1$). The marginal increase in the incidence of hepatocellular carcinomas and adenomas in male $B6C3F_1$ mice was concluded to be equivocal evidence in the NCI (1980) report on its bioassay.
- IARC (1983) has classified fluometuron in Group 3: This chemical cannot be classified as to its carcinogenicity for humans.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), fluometuron may be classified in Group D: not classified. This category is used for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA/OPP previously calculated an ADI of 0.008 mg/kg/day based on a NOAEL of 7.5 mg/kg/day in a 90-day feeding study in rats (Foglemann, 1965a) and an uncertainty factor of 1,000 (used because of data gaps). This has been updated to 0.013 mg/kg/day, based on a 2-year feeding study in rats using a NOAEL of 12.5 mg/kg/day and an uncertainty factor of 1,000.
- Tolerances have been established for negligible residues of fluometuron in or on cottonseed and sugar cane at 0.1 ppm (U.S. EPA, 1985a). A tolerance is a derived value based on residue levels, toxicity data, food consumption levels, hazard evaluation and scientific judgment, and it is the legal maximum concentration of a pesticide in or on a raw agricultural commodity or other human or animal food (Paynter et al., undated).

VII. ANALYTICAL METHODS

- Analysis of fluometuron is by a high-performance liquid chromatographic (HPLC) method applicable to the determination of certain carbamate and urea pesticides in water samples (U.S. EPA, 1986b). This method requires a solvent extraction of approximately 1 liter of sample with methylene chloride using a separatory funnel. The methylene chloride extract is dried and concentrated to a volume of 10 mL or less. HPLC is used to permit the separation of compounds and measurement is conducted with a UV detector. This method has been validated in a single laboratory and estimated detection limits have been determined for the analytes in the method, including fluometuron. The estimated detection limit is 0.10 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular activated carbon (GAC) adsorption will remove fluometuron from water.

- Whittaker (1980) experimentally determined adsorption isotherms for fluometuron on GAC.

- Whittaker (1980) reported the results of GAC columns operating under bench-scale conditions. At a flow rate of 0.8 gpm/sq ft and an empty bed contact time of 6 minutes, fluometuron breakthrough (when effluent concentration equals 10% of influent concentration) occurred after 1,640 bed volumes (BV). When a bi-solute solution of fluometuron diphenamide was passed over the same column, fluometuron breakthrough occurred after 320 BV.

- GAC adsorption appears to be the most promising treatment technique for the removal of fluometuron from contaminated water. However, selection of individual or combinations of technologies to attempt fluometuron removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

FONOFOS

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

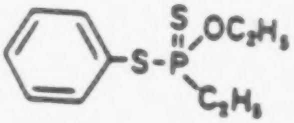
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 944-22-9

Structural Formula



O-Ethyl-S-phenylethylphosphonodithioate

Synonyms

- Difonate; Difonatal; Dyfonate®; ENT 25, 796; Fonophos; Stauffer N2790 (Meister, 1983).

Uses

- Soil insecticide (Meister, 1983).

Properties (Windholz et al., 1983; TDB, 1985)

Chemical Formula	$C_{10}H_{15}OS_2P$
Molecular Weight	246.32
Physical State (25°C)	Light yellow liquid
Boiling Point	130°C
Melting Point	--
Vapor Pressure (25°C)	2.1×10^{-4} mm Hg
Specific Gravity (20°C)	1.154
Water Solubility (25°C)	Practically insoluble
Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Fonofos has been found in tailwater pit sediment and water samples. Monitoring studies conducted in 1973 and 1974 in Haskell County, Kansas, showed that the highest concentrations found were 770 ppb for sediment and 5.9 ppb for water during 1974. Mean peak concentrations were highest in June and July (Kadoum and Mock, 1978).

- Fonofos (Dyfonate) has been found in Iowa ground water; a typical positive sample found was 0.1 ppb (Cohen et al., 1986).

- Fonofos has ben found in 194 of 3,399 surface water samples analyzed and in 2 of 570 ground water samples (STORET, 1988). Samples were collected from 183 surface water locations and 456 ground water locations. The 85th percentile of all non-zero samples was 0.32 ug/L in surface water and 8,900 ug/L in ground water sources. The maximum concentration found in surface water was 33 ug/L and in ground water it was 8,900 ug/L. Fonofos was found in surface water in Iowa, Illinois, Michigan and Ohio, and in ground water in Alabama. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Under aerobic conditions, fonofos at 10 ppm was degraded at a moderate rate with a half-life ranging from 3 to more than 16 weeks in soils varying in texture from loamy sand to clay loam to peat (McBain and Menn, 1966; Hoffman et al., 1973; Hoffman and Ross, 1971; Miles et al., 1979). The major degradate identified was O-ethylethane phosphonothioic acid; other degradates identified included fonofos oxon, O-ethylethane phosphonic acid, O-ethyl O-methylethyl phosphonate, diphenyl disulfide, methylphenyl sulfoxide, and methylphenyl sulfone (Hoffman et al., 1973; Hoffman and Ross, 1971). The soil fungus, Rhizopus japonicus rapidly degraded ^{14}C-fonofos to yield dyfoxon, thiophenol, ethylethoxy phosphonic acid and methylphenyl sulfoxide (Lichtenstein et al., 1977).

- Fonofos is relatively immobile in a silt loam and sandy loam soil but relatively mobile in quartz sand. After 7 to 12 inches of water were added to 7-inch soil columns, 2 to 9% of the applied ^{14}C-fonofos leached from the treated soil layer in Plano silt loam and Fox fine sandy loam columns. When a quartz sand was leached with 7 inches of water, 50% of the applied radioactivity was detected in the leachate. Dyfoxon, a fonofos degradate, and two unidentified compounds were found in the leachate of the silt loam soil (Lichtenstein et al., 1972).

- Fonofos is relatively mobile in runoff water from loam sand. After 30 days, only 0.54 to 1.2% of the applied ^{14}C-fonofos was recovered in runoff water from drenching a Sorrento loam soil on an inclined plane at a 15-degree slope. Fonofos accounted for most of the recovered radioactivity, which was primarily adsorbed to the silt fraction (Hoffman et al., 1973).

- Fonofos is not volatile from soil but is fairly volatile from water. Within 24 hours after application, 15 to 16% of the ^{14}C-fonofos applied volatilized from soil water (a suspension of fine sand in tapwater or tapwater alone; 1% volatilized from a silt loam soil alone).

^{14}C-Fonofos volatilized from soil water with a half-life of 5 days; 80% of the applied radioactivity was volatilized at the end of 10 days (Lichtenstein and Schulz, 1970).

° In the field, fonofos dissipated with a half-life of 28 to 40 days when either a 10% G or a 4 lb/gal EC formulation was applied at 4.8 to 10 lb ai/A to a sandy loam and two silt loam soils (Kiigemagi and Terriere, 1971; Schulz and Lichtenstein, 1971; Talekar et al., 1977). Using a root maggot bioassay, toxic fonofos residues in a sandy loam field soil were detected up to 17 weeks after the 10% G formulation was applied at 2 to 5 lb ai/A. Residues were detected up to 28 weeks after treatment when the same soil was maintained in a greenhouse (Ahmed and Morrison, 1972).

III. PHARMACOKINETICS

Absorption

° McBain et al. (1971) administered ^{14}C-phenyl-labeled fonofos (99% purity, dissolved in corn oil) orally to albino rats (two/dose) at doses of 2, 4 or 8 mg/kg. Only 7% of the label was recovered in feces, indicating that absorption was nearly complete (about 93%). Hoffman, et al. (1971) reported essentially identical results in rats dosed with 0.8 mg/kg fonofos. Measurements of urinary, fecal and biliary excretion indicated that about 80 to 90% of the dose was absorbed from the gastrointestinal tract.

° Hoffman et al. (1971) administered single oral doses of ^{35}S-labeled fonofos (2.0 mg/kg; 99% purity) to rats. About 32% of the label was excreted in feces. Measurement of biliary excretion indicated that 15% of the label in the feces came from the bile. The authors concluded that about 17% had not been absorbed.

Distribution

° Hoffman et al. (1971) administered ^{35}S-labeled fonofos (2.0 mg/kg, 13.4 mCi/mmol; 99% purity) to rats by gavage (in safflower oil); the levels of label in blood and tissues were measured for 16 days. Higher levels of radioactivity were found in the kidneys, blood, liver and intestines, and lower levels were found in bone, brain, fat, gonads and muscle. Concentration values at 2 days ranged from about 400 ppb in the kidneys to about 70 ppb in other tissues. All values were 10 ppb or lower by day 8. Tissue levels declined in first-order fashion, with near total (99.3%) elimination during 2 to 16 days after dosing.

Metabolism

° McBain et al. (1971) administered single oral doses of 2, 4 or 8 mg/kg of ethyl or phenyl-^{14}C-labeled fonofos (97.5% or 99% purity) to male albino rats (two/dose). Only 2.6 to 7.1% was recovered as unchanged fonofos in the urine. The remainder was converted to a variety of terminal metabolites, including: 0-ethylethane phosphonothioic acid, 0-ethylethane phosphonic acid, and 0-conjugates of 3- and 4-(hydroxphenyl)methyl sulfone. McBain et al. (1971) reported that fonofos was converted by rat liver microsomes in vitro to the more toxic fonofos oxon, but only traces of this compound were excreted by the intact animal.

Excretion

- McBain et al. (1971) administered single oral doses of 2, 4 or 8 mg/kg of ^{14}C-labeled fonofos (97.5% or 99% purity) orally to male albino rats (two rats/dose). When the label was on the phenyl ring, recovery of label was 90.7% in urine and 7.4% in feces. When the label was on the ethyl group, recovery of label was 62.8% in urine and 31.8% in feces. Of this fecal label, 15.3% was found to be excreted in the bile.

- Hoffman et al. (1971) dosed rats orally with ^{14}C-ethyl-labeled fonofos (0.8 mg/kg; 98% purity). After 15 days, average recovery of label was 91% in urine, 7.4% in feces and 0.35% in expired air. Essentially all of the excretion occurred within 4 days. In rats dosed with ^{35}S-labeled fonofos (2 mg/kg; 99% purity), average recovery of label after 4 days was 62.5% in the urine, 31.8% in feces and 0.1% in expired air. Bile duct cannulation studies indicated that about 15% of the label in feces arose from biliary excretion.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- The Pesticide Incident Monitoring System (PIMS) database reported 21 cases between 1966 and 1979 of human toxicity resulting from exposure to fonofos. Fourteen of the cases involved fonofos only, and seven involved mixtures. Two fatalities occurred, and four individuals required medical treatment. No quantitative exposure data and no description of adverse effects were provided (U.S. EPA, 1979).

- One reported case of accidental ingestion involved a 19-year old woman who ate pancakes prepared with ingredients containing fonofos. No quantitative estimate of the dose level was provided. The individual developed nausea, vomiting, salivation, sweating and suffered cardio-respiratory arrest. She was treated at a hospital and was found to have muscle fasciculation, blood pressure of 64/0 mm Hg, a pulse rate of 46, pinpoint pupils, and profuse salivary and bronchial secretions. The patient also developed a pancreatic pseudocyst. The woman was discharged after 2 months of treatment. A second individual who also ate the contaminated pancakes died (Hayes, 1982).

Long-term Exposure

- No information on the long-term exposure effects of fonofos on humans was found in the available literature.

Animals

Short-term Exposure

- Reported values for the oral LD_{50} of fonofos for female rats range from 3.2 to 7.9 mg/kg, and values for male rats range from 6.8 to 18.5 mg/kg (Horton, 1966a,b; Dean, 1977).

- Horton (1966a) administered single oral doses of fonofos (purity not specified) to rats (strain not specified). Doses of 1.0 or 2.15 mg/kg did not produce visible symptoms. Doses of 4.6 to 46 mg/kg elicited rapid appearance of fasciculations and tremors, salivation, exophthalmia and labored respiration, with females being somewhat more sensitive than males. Gross autopsy of animals that died revealed congested liver, kidneys and adrenals and lung erythema. Autopsy of survivors showed no effects. Based on gross changes, a No-Observed-Adverse-Effect Level (NOAEL) of 2.15 mg/kg was identified by this study.

- Cockrell et al. (1966) fed fonofos in the diet to dogs at levels of 0 or 8 ppm for 5 weeks. These levels were stated by the authors to be equivalent to 0 and 0.2 mg/kg/day. Plasma and red blood cell cholinesterase (ChE) were measured at 2 and 4 weeks; organ weights, brain ChE and changes in gross pathology were measured at termination (5 weeks). Following treatment, no systemic toxicity was observed; brain and plasma or red blood cell cholinesterase levels were unaffected. No other details were provided. This study identified a NOAEL of 8 ppm (0.2 mg/kg/day).

- In a demyelination study, groups of 10 adult hens each received technical fonofos (99.8% pure) in the diet for 46 days (Woodard and Woodard, 1966). Levels fed were equivalent to 0, 2, 6.32 or 20 mg/kg/day. Only hens at 20 mg/kg showed impairment of locomotion and equilibrium, and one showed histological evidence of possible demyelination of the peripheral nerves. A NOAEL for demyelination of 6.32 mg/kg/day was indicated by the study.

Dermal/Ocular Effects

- Reported dermal LD_{50} values of fonofos for the rabbit (both sexes) ranged from 121 to 147 mg/kg (Horton, 1966a,b). However, Dean (1977) determined a different LD_{50} in rabbits: 25 mg/kg for females and 100 mg/kg for males.

- Instillation of 0.1 mL undiluted fonofos (about 23 mg/kg/day) in one eye of each of three rabbits caused negligible local irritation, but was lethal to all within 24 hours (Horton, 1966a,b; Dean, 1977).

- Dean (1977) applied 0.5 mL undiluted fonofos to closely clipped intact skin of rabbits; no dermal irritation was reported but all animals died within 24 hours.

- Horn et al. (1966) applied fonofos (10% granular) to the intact or abraded skin of New Zealand rabbits (five/sex/dose; the five animals included both normal and abraded skin animals) 5 days per week for 3 weeks at doses of 0, 35 or 70 mg/kg. Following treatment, dermal effects, general appearance and behavior, hematology, organ weights, cholinesterase levels, gross pathology and histopathology were evaluated. No difference was observed in any of the responses between the intact or abraded skin animals. One normal and one abraded skin males and one normal skin female died in the 70 mg/kg group; and one intact skin male died in the 35 mg/kg group. No irritation of the skin was observed at any dose tested for either intact or abraded skin. In males, adrenal weights were increased by about 50% at 35 mg/kg, and by 70% at 70 mg/kg (p value not given). Similar but smaller (15 to 20%) increases in adrenal weights were seen in females. No hematological effects were observed at any dose tested. No histopathological changes occurred except slight to moderate liver glycogen depletion at 70 mg/kg. Reductions were observed in red blood cell, plasma and brain cholinesterase activity for both sexes of the treated groups. Only values for abraded skin were reported. At 35 mg/kg, ChE in red blood cells was inhibited 70% (for both sexes), while plasma ChE levels were inhibited 74% (males) and 91% (females), and brain ChE was inhibited 66% (males) and 89% (females). At 70 mg/kg, ChE in red blood cells was inhibited 36% (males) and 45% (females). ChE in plasma was inhibited 67% inhibited for both sexes. ChE in brain was inhibited 59% (males) and 57% (females).

Long-term Exposure

- Daily oral doses of fonofos in corn oil (at 0, 2, 4 or 8 mg/kg/day) for 90 days failed to elicit delayed neurotoxicity in adult hens (Miller et al., 1979, abstract only). A minimum NOAEL of 8 mg/kg/day for delayed neurotoxicity was indicated by these reported results.

- In a similar experiment (Cockrell et al., 1966), rats were fed diets containing difonate at 0, 10, 31.6 or 100 ppm for 13 weeks. Based on the assumption that 1 ppm in the diet is equivalent to 0.05 mg/kg/day, these doses correspond to 0, 0.5, 1.58 or 5 mg/kg/day (Lehman, 1959). Cholinesterase was measured in serum and red blood cells before and after exposure, and brain ChE was measured at termination. At 100 ppm, there was significant inhibition of ChE in serum (70%, females only), red blood cells (85%, females only) and brain (51% to 60%, both sexes). Decreases of over 50% in red blood cell ChE in both males and females were reported at the 31.6-ppm level. At 10 ppm, the largest difference detected was a 23% decrease in red blood cell ChE in females; the authors did not consider this to be significant. All other ChE measurements at this dose were comparable between exposed and control animals. Other observations were negative for compound effect, and there were no histopathological findings. Based on ChE inhibition, the NOAEL in rats was identified as 10 ppm (0.5 mg/kg/day).

- Cockrell et al. (1966) fed fonofos in the diet to dogs at levels of 0, 16, 60 or 240 ppm for 14 weeks. These levels were stated by the authors to be equivalent to 0, 0.4, 1.5 or 6 mg/kg/day. Dogs showed increased lacrimation and salivation plus convulsions (at

16 ppm), bloody diarrhea (at 60 ppm) or tremors and anxiety and increased liver weight (at 240 ppm). At 16 ppm, there was about 60% ChE inhibition in erythrocytes and slight ChE inhibition in brain (female only). At 60 ppm, ChE in red blood cells was inhibited 60% or more, and plasma ChE was decreased about 20% (in males only) at week 13. At the high dose (240 ppm), ChE was nearly totally inhibited in red blood cells; about 50% inhibited in plasma; and moderately inhibited in brain. Based on cholinesterase inhibition and systemic toxicity, a Lowest-Observed-Adverse-Effect Level (LOAEL) of 16 ppm (0.4 mg/kg/day), the lowest dose tested, was identified.

- Pure-bred beagle dogs were fed fonofos in the diet for 2 years (Woodard et al., 1969). Groups of four males and four females each received 0, 16, 60 or 240 ppm fonofos. Based on the assumption that 1 ppm in the diet is equivalent to 0.025 mg/kg/day, these doses correspond to 0, 0.4, 1.5 or 6 mg/kg/day (Lehman, 1959). After 14 weeks, the low dose (16 ppm) was reduced to 8 ppm (0.2 mg/kg/day), and this dose level was maintained for the duration of the study. Cholinesterase levels in plasma were inhibited about 50% at 240 ppm, about 25% to 50% at 60 ppm, and were not different from controls at the low dose (16 or 8 ppm). In red blood cells, ChE levels were inhibited almost completely at the 240-ppm level and about 65% at 60 ppm. In animals receiving 16 ppm for 14 weeks, ChE in red blood cells was inhibited about 30%. After reduction of the dose to 8 ppm, ChE levels returned to values comparable to controls. At sacrifice, no inhibition of ChE in brain was detected at any dose level. At 240 ppm, nervous, apprehensive behavior and tremors were seen, and three dogs died, each with marked acute congestion of tissues and hemorrhage of the small intestinal mucosa. At this dose level, also, serum alkaline phosphatase was increased, as were liver weights. Histopathological examination of animals receiving 240 ppm revealed a marked increase in basophilic granulation of the myofibril of the inner layer of the muscularis of the small intestine, and there were slight changes in the liver. At 60 ppm, increased liver weight was observed. At the low dose (16/8 ppm), the only effect was a single brief episode of fasciculation in one male dog at 5 months. The author judged that this could not be ascribed with certainty to fonofos exposure. For this study, the NOAEL for ChE inhibition and for systemic toxicity was 8 ppm (0.2 mg/kg/day).

- Albino rats received fonofos in the diet for 2 years at 0, 10, 31.6 or 100 ppm (0, 0.5, 1.58 or 5 mg/kg/day, Lehman, 1959) (Banerjee et al., 1968). Fonofos was judged not to have affected survival, food intake, body weight gain, organ weights or gross and histopathological findings. At 100 ppm, females showed tremors and nervous behavior, and males had reduced hemoglobin and packed-cell volume. At 100 ppm, ChE was markedly decreased in plasma (50 to 75%), red blood cells (close to 100%) and brain (about 40%, in females only). At 31.6 ppm, there was moderate (about 50%) inhibition of ChE in red blood cells and plasma (at weeks 26 and 52 only). At 10 ppm, no decrease in ChE was seen in brain or red blood cells, and no effect was seen in plasma, except for a moderate decrease (40 to 56%) in males at weeks 19 and 26 only. Based on cholinesterase inhibition, a NOAEL of 10 ppm (0.5 mg/kg/day) is identified.

Reproductive Effects

- Woodard et al. (1968) exposed three generations of rats to dietary fonofos at 0, 10 or 31.6 ppm. Based on the assumption that 1 ppm in the diet of a rat is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.5 or 1.58 mg/kg/day. No differences were detected in exposed dams with respect to mortality, body weight or uterine implantation sites. No effects were seen in offspring on conception ratio, litter size, number of live-born and still-born, litter weight and weanling survival. Skeletal and visceral examination of offspring revealed no evidence of developmental defects. A NOAEL of 31.6 ppm (1.58 mg/kg/day, the highest dose tested) was identified.

Developmental Effects

- Groups of pregnant mice each received 10 daily doses of fonofos by gavage (0, 2, 4, 6 or 8 mg/kg/day) on gestational days 6 through 15 (Minor et al., 1982). At 8 mg/kg/day, maternal food intake and body weight gain were decreased. At 6 mg/kg/day, two dams experienced tremors and died. Increased incidences of variant ossifications of the sternebrae (8 mg/kg/day) and a slight dilatation of the fourth ventricle of the brain (4 and 8 mg/kg/day) were observed, but the authors did not interpret this as evidence of teratogenicity. Based on these findings, the NOAEL for fetotoxicity identified in this study was 2 mg/kg/day. The teratogenic NOAEL identified for this study was 8 mg/kg/day.

Mutagenicity

- Fonofos, with or without metabolic activation, was not mutagenic in each of five microbial assay systems (the Ames (*Salmonella typhimurium*) test; reverse mutation in an *Escherichia coli* strain; mitotic recombination in the yeast, *Saccharomyces cerevisiae* D3; and differential toxicity assays in strains of *E. coli* and *Bacillus subtilis*) and in a test for unscheduled DNA synthesis in human fibroblast (WI-38) cells (Simmon, 1979).

Carcinogenicity

- Groups of 30 male and 30 female CD albino rats (Charles River) each received 0, 10, 31.6 or 100 ppm fonofos in the diet (0, 0.5, 1.58 or 5 mg/kg/day) for 2 years (Banerjee et al., 1968). Based on gross and histological examination, the authors detected no carcinogenic effects.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption by a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for fonofos. It is therefore recommended that the adjusted DWEL for a 10-kg child of 0.02 mg/L (20 ug/L) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

No information was found in the available literature that was suitable for determination of the Ten-day HA value for fonofos. It is therefore recommended that the adjusted DWEL for a 10-kg child of 0.02 mg/L (20 ug/L) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

No information was found in the available literature that was suitable for determination of the Longer-term HA value for fonofos. It is therefore recommended that the adjusted DWEL for a 10-kg child of 0.02 mg/L (20 ug/L) be used at this time as a conservative estimate of the Longer-term HA and that the DWEL of 0.07 mg/kg (70 ug/L) be used for a 70-kg adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor. From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in dogs by Woodard et al. (1969) has been selected to serve as the basis for the Lifetime HA for fonofos. Dogs received dietary fonofos at 0, 16, 60 or 240 ppm (0, 0.4, 1.5 or 6 mg/kg/day) for 14 weeks. Marginal (about 30%) inhibition of ChE was noted in red blood cells at the 16-ppm level; this dose was reduced to 8 ppm (0.2 mg/kg/day). Following dose reduction, ChE levels returned to control. At 60 ppm, dogs showed increased liver weights and significant inhibition (25 to 65%) of ChE activity in plasma and erythrocytes. At 240 ppm, there was increased ChE inhibition and increased mortality. There were no toxic effects in dogs at 8 ppm (0.2 mg/kg/day), with the possible exception of one brief episode of fasciculation in one dog at 5 months. This was not judged to be significant, and a NOAEL of 8 ppm (0.2 mg/kg/day) was identified. The 2-year feeding study in rats by Bannerjee et al. (1968) has not been selected, since rats appear to be less sensitive than dogs when doses are calculated on a body weight (mg/kg) basis.

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.2 \text{ mg/kg/day})}{(100)} = 0.002 \text{ mg/kg/day}$$

where:

0.2 mg/kg/day = NOAEL, based on absence of systemic toxicity or ChE inhibition in dogs exposed to fonofos in the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guideline for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.002 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.07 \text{ mg/L } (70 \text{ ug/L})$$

where:

0.002 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption by an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.07\ \text{mg/L})\ (20\%) = 0.014\ \text{mg/L}\ (10\ \text{ug/L})$$

where:

0.07 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Groups of 30 male and 30 female albino rats (Charles River, Cesarean-derived) each received 0, 10, 31.6 or 100 ppm fonofos in the diet (0, 0.5, 1.58 or 5 mg/kg/day) for 2 years (Banerjee et al., 1968). Based on gross and histological examination, the authors detected no carcinogenic effect.
- IARC (1982) has not evaluated the carcinogenic potential of fonofos.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), fonofos may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- No existing criteria, guidelines or standards for oral exposure to fonofos were located.
- The U.S. EPA Office of Pesticide Programs (OPP) has calculated an ADI of 0.002 mg/kg/day for fonofos. This was based on a NOAEL of 0.2 mg/kg/day (8 ppm) for both ChE inhibition and systemic effects, in a 2-year feeding study in dogs (Woodard et al., 1969), and an uncertainty factor of 100.
- The Threshold Limit Value (TLV) for fonofos is 100 ug/m^3 (ACGIH, 1984).
- The U.S. EPA (1985) has established tolerances for fonofos in or on raw agricultural commodities that range from 0.1 to 0.5 ppm.

VII. ANALYTICAL METHODS

- Analysis of fonofos is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus-containing pesticides in water samples (Method #507, U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen-phosphorus detector. The method detection limit has not been determined for fonofos, but it is estimated that the detection limits for analytes included in this method are in the range of 0.1 to 2 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information on treatment technologies used to remove fonofos from contaminated water was found in the available literature.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

GLYPHOSATE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

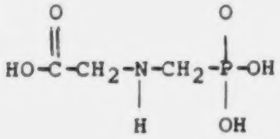
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1071-83-6

Structural Formula



$$HO-\overset{\overset{O}{\|}}{C}-CH_2-\underset{\underset{H}{|}}{N}-CH_2-\overset{\overset{O}{|}}{\underset{\underset{OH}{|}}{P}}-OH$$

Glycine, N-(Phosphonomethyl)

Synonyms

- Active ingredient (glyphosate) in Rodeo®, Roundup®, Landmaster®, Shakle®, Roundup L & G®, Polado®.

Uses

- Herbicide for control of grasses, broad leaved weeds and woody brush (U.S. EPA, 1986b).

Properties (Meister, 1983)

Chemical Formula	$C_3H_8NO_5P$
Molecular Weight	169.07
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	200°C (decomposes)*
Density	0.5 g/mL (bulk density of dried technical)*
Vapor Pressure	--
Water Solubility	11.6 g/L*
Log Octanol/Water Partition Coefficient	0.0006-0.0017*
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

* Monsanto, 12/13/87

Occurrence

- No glyphosate was detected in 6 surface water samples or 98 groundwater samples taken from 3 surface water stations and 97 groundwater stations, respectively (STORET, 1988).

Environmental Fate

- Biodegradation is considered the major fate process affecting glyphosate persistence in aquatic environments (Reinert and Rodgers, 1987). Glyphosate is biodegraded aerobicaly and anaerobically by microorganisms present in soil, water, hydrosoil and activated sludge.

- ^{14}C-Glyphosate (94% glyphosate, 5.9% aminomethylphosphonic acid) and aminomethylphosphonic acid were stable in sterile buffered water at pH 3, 6, and 9 during 32 days of incubation in the dark at 5 and 35°C (Brightwell and Malik, 1978).

- ^{14}C-Glyphosate (94% glyphosate, 5.9% aminomethylphosphonic acid) was adsorbed to Drummer silty clay loam, Ray silt. Spinks sandy loam, Lintonia sandy loam, and Cattail Swamp sediment with Freundlich-K values of 62, 90, 70, 22, and 175, respectively (Brightwell and Malik, 1978). For each soil preparation, the maximum percentages of applied glyphosate desorbed were 5.3, 3.7, 3.6, 11.5, and 0.9%, respectively. At concentrations ranging from 0.21 to 50.1 ppm, ^{14}C-Glyphosate was highly adsorbed to five soils, with organic matter contents ranging from 2.40 to 15.50% (Monsanto Company, 1975). Adsorption of glyphosate ranged from 71 (Soil E, 2.4% organic matter, pH 7.29) to 99% (Soil C, 15.5% organic matter, pH 5.35).

- ^{14}C-Glyphosate (94% glyphosate, 5.9% aminomethylphosphonic acid) was slightly mobile to relatively immobile, with less than 7% of the applied ^{14}C detected in the leachate from 30-cm silt, sand, clay, sandy clay loam, silty clay loam, and sandy loam soil columns eluted with 20 inches of water (Brightwell and Malik, 1978). Aged (30 days) ^{14}C-glyphosate residues were relatively immobile in silt, clay and sandy clay loam soils with less than 2% of the radioactivity detected in the leachate following elution with 20 inches of water. Both glyphosate and aminomethylphosphonic acid were detected in the leachate of aged and un-aged soil columns.

III. PHARMACOKINETICS

Absorption

- Feeding studies with chickens, cows and swine showed that ingestion of up to 75 ppm glyphosate resulted in nondetectable glyphosate residue levels (<0.05 ppm) in muscle tissue and fat (Monsanto Company, 1983). The duration of exposure was for 30 days. Glyphosate residue levels were not detectable (<0.025 ppm) in milk and eggs from cows and chickens on diets containing glyphosate.

Distribution/Metabolism

- The distribution, metabolism and retention of glyphosate by the tissues appear to be minimal since 60 to 90% of a single oral dose is rapidly eliminated unchanged in the feces (Duerson and Sipes, 1987).

Excretion

- After a single oral or intraperitoneal dose, less than 1% of the administered dose was retained after 120 hours of treatment (U.S. EPA, 1986b). In rats fed 1, 10 or 100 ppm of ^{14}C-glyphosate for 14 days, a steady-state equilibrium between intake and excretion of label was reached within about 8 days. The amount of radioactivity excreted in the urine decreased rapidly after withdrawal of treatment. Ten days after withdrawal, radioactivity was detectable in the urine and feces of rats fed 10 or 100 ppm of the test diet. Minimal residues of 0.1 ppm or less remained in the tissues of high-dose rats after 10 days of withdrawal. No single tissue showed a significant difference in the amount of label retained.

IV. HEALTH EFFECTS

Humans

- Glyphosate, a widely utilized herbicide, was evaluated for acute irritation, cumulative irritation, photoirritation and allergic and photoallergic contact potential in 346 volunteers. The herbicide was less irritant than a standard liquid dishwashing detergent and a general all purpose cleaner. There was no evidence for the induction of photoirritation, allergic or photoallergic contact dermatitis. Ten percent glyphosate in water is proposed as a diagnostic patch test concentration (Maibach, 1986).

Animals

Short-term Exposure

- An oral LD_{50} of 5,600 mg/kg in the rat is reported for glyphosate (Monsanto Company, 1985).

- Bababunmi et al. (1978) reported that daily intraperitoneal administration of 15, 30, 45 or 60 mg/kg to rats for 28 days resulted in reduced daily body weight gain, decreased blood hemoglobin, decreased red blood cell count and hematocrit values and elevated levels of serum glutamic-pyruvic transaminase and leucine-amino peptidase during the experimental period. The investigators did not specify the dose levels at which these effects were observed.

Dermal/Ocular Effects

- A dermal LD_{50} for glyphosate in the rabbit was reported to be >5,000 mg/kg (Monsanto Company, 1985).

Long-term Exposure

- In subchronic studies reported by the Weed Science Society of America (1983), technical-grade glyphosate was fed to rats and dogs at dietary levels of 200, 600 or 2,000 ppm for 90 days. Mean body weights, food consumption, behavioral reactions, mortality, hematology, blood chemistry and urinalysis did not differ significantly from controls. There were no relevant gross or histopathological changes. No other details or data were provided.

- Bio/dynamics, Inc. (1981a) conducted a study in which glyphosate was administered in the diet to four groups of Sprague-Dawley rats (50/sex/dose) at dose levels of 0, 3.1, 10.3 or 31.5 mg/kg/day to males or 0, 3.4, 11.3 or 34.0 mg/kg/day to females. After 26 weeks, body weight, organ weight, organ-to-body weight ratios and hematological and clinical chemistry parameters were evaluated. No significant differences between control and exposed animals were observed at any dose level.

- Glyphosate was administered to mice at dietary levels of 5,000, 10,000 and 50,000 ppm for 3 months. Decreased body weight gains were observed in the high-dose group. No treatment-related effects in pathologic or histopathologic evaluations were observed. The no-effect level was considered to be 10,000 ppm (Monsanto Company, 1985).

- Beagle dogs were fed glyphosate at dietary concentrations of 30, 100 or 300 ppm for 2 years. No evidence of treatment-related chronic or carcinogenic effects were observed. The no-effect level was considered to be 300 ppm (Monsanto Company, 1985).

Reproductive Effects

- Bio/dynamics, Inc. (1981b) investigated the reproductive toxicity of glyphosate in rats. The glyphosate (98.7% purity) was administered in the diet at dose levels of 0, 3, 10 or 30 mg/kg/day to Charles River Sprague-Dawley rats for three successive generations. Twelve males and 24 females (the F_0 generation) were administered test diets for 60 days prior to breeding. Administration was continued through mating, gestation and lactation for two successive litters (F_{1a}, F_{1b}). Twelve males and 24 females from the F_{1b} generation were retained at weaning for each dose level to serve as parental animals for the succeeding generation. The following indices of reproductive function were measured: fetal, pup and adult survival; parental and pup body weight; food consumption; and mating, fertility or gestation. Necropsy and histopathologic evaluation were performed as well. No compound-related changes in these parameters were observed when compared to controls, although an addendum to the pathological report for this study reported an increase in unilateral focal tubular dilation of the kidney in the male F_{3b} pups when compared to concurrent controls. Based on data from this study, the authors concluded that the highest dose tested (30 mg/kg/day) did not affect reproduction in rats under the conditions of the study.

Developmental Effects

- Glyphosate was administered to pregnant rabbits by gavage at dose levels of 75, 175 or 350 mg/kg/day on days 6 through 27 of gestation (Monsanto Company, 1982a). No evidence of fetal toxicity or birth defects in the offspring was observed. However, at dose levels of 350 mg/kg/day, death, soft stools, diarrhea and nasal discharge were observed in the animals.

- No teratogenic effects were observed in the offspring of rats administered glyphosate by gavage at dosage levels of 300, 1,000 and 3,500 mg/kg/day on days 6 through 19 of gestation. Toxic effects were noted in the high-dose treated animals and their offspring (Monsanto Company, 1985).

Mutagenicity

- The Monsanto Company (1985) reported that glyphosate did not cause mutation in microbial test systems. A total of eight strains (seven bacterial and one yeast), including five *Salmonella typhimurium* strains and one strain of *Bacillus subtilis*, *Escherichia coli* and *Saccharomyces cerevisiae*, were tested. No mutagenic effects were observed in any strain.

- Njagi and Gopalan (1980) found that glyphosate did not induce reversion mutations in *Salmonella typhimurium* histidine auxotrophs.

Carcinogenicity

- Bio/dynamics, Inc. (1981b) conducted a study to assess the oncogenicity of glyphosate (98.7% purity). The chemical was given in the diet to four groups of Sprague-Dawley rats at dose levels of 0, 3.1, 10.3 or 31.5 mg/kg/day to males or 0, 3.4, 11.3 or 34.0 mg/kg/day to females. After 26 months, animals were sacrificed and tissues were examined for histological lesions. A variety of benign and malignant tumors were observed in both the treated and control groups, the most common tumor occurring in the pituitary of both sexes and in the mammary glands of females. The total number of rats of both sexes that developed tumors (benign and malignant) was 72/100 (low dose), 79/100 (mid dose), 85/100 (high dose) and 87/100 (control). An increased rate of interstitial cell tumors of the testes was reported in the high-dose males when compared to concurrent controls (6/50 versus 0/50), but this was not considered to be related to compound administration. Based on the data from this study, the authors concluded that the highest dose level tested (31.5 and 34.0 mg/kg/day for males and females, respectively) was not carcinogenic in rats.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\underline{\quad}\ \text{L/day})} = \underline{\quad}\ \text{mg/L}\ (\underline{\quad}\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for glyphosate. It is, therefore, recommended that the Ten-day HA value of 20 mg/L be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The teratology study in pregnant rabbits has been selected to serve as the basis for determination of the Ten-day HA for the 10-kg child. In this study, pregnant rabbits that received glyphosate at dose levels of 0, 75, 175 or 350 mg/kg/day on days 6 through 27 of gestation showed effects at 350 mg/kg/day; however, no treatment-related effects were reported at lower dose levels. The No-Observed-Adverse-Effect-Level (NOAEL) identified in this study is, therefore, 175 mg/kg/day.

Using a NOAEL of 175 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(175\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 17.5\ \text{mg/L}\ (20{,}000\ \text{ug/L})$$

where:

175 mg/kg/day = NOAEL, based on absence of altered physical changes and mortality in rabbits.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

No information was found in the available literature that was suitable for determination of the Longer-term HA value for glyphosate. It is, therefore, recommended that the adjusted DWEL for a 10-kg child (1 mg/L) and 4 mg/L for an adult be used at this time as a conservative estimate of the Longer-term HA value.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Bio/dynamics (1981b) has been selected to serve as the basis for determination of the Lifetime HA value for glyphosate. In this study, the reproductive toxicity of glyphosate in rats was investigated over three generations. Even though no compound-related changes in the reproductive indices were observed when compared to controls at a dose level of 30 mg/kg/day, there were pathological changes of renal focal tubular dilation in male F_{3b} weanling rats at this level. Therefore, the lower dose level of 10 mg/kg/day was identified as the NOAEL.

Using a NOAEL of 10 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(10\ \text{mg/kg/day})}{(100)} = 0.1\ \text{mg/kg/day}$$

where:

10 mg/kg/day = NOAEL, based on absence of renal focal tubular dilation in rats.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.1\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 3.5\ \text{mg/L}\ (4{,}000\ \text{ug/L})$$

where:

0.1 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (3.5\ \text{mg/L})\ (20\%) = 0.70\ \text{mg/L}\ (800\ \text{ug/L})$$

where:

4.0 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), glyphosate may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

- The evidence of carcinogenicity in animals is considered equivocal by the Science Advisory Board (Pesticides), and has been classified in Category D [Office of Pesticide Programs has requested the manufacturer to conduct another study in animals (U.S. EPA, 1986b)].

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- No other criteria, guidelines or standards were found in the available literature pertaining to glyphosate.

- Tolerance of 0.1 ppm has been established for the combined residues of glyphosate and its metabolite in or on raw agricultural commodities resulting from the use of irrigation water following applications of glyphosate herbicide around aquatic sites (U.S. EPA, 1985).

VII. ANALYTICAL METHODS

- A method for glyphosate has been developed for ODW by EMSL-CI (U.S. EPA, 1988). Other methods are available for glyphosate. However, this modification has been directed toward water, since glyphosate is used as an aquatic herbicide and the media of concern is drinking water. In this procedure a water sample is filtered and a samll aliquot (200 ul) is injected into a referse phase high pressure liquid chromatograph column. Separation is by isocratic elution. Post-column derivatization involves oxidation of the glyphosate to glycine with reaction to o-phthalaldehyde to form a sensitive fluorophore. The method detection limit for this procedure for single laboratory validation is 6 ug/L for tap water, and 9 ug/L for ground water. Across four concentrations with 8 data points for each type of water (tap water, ground water), recoveries ranged from 95 to 110%, with a relative standard deviation ranging from 2 to 12%.

VIII. TREATMENT TECHNOLOGIES

- No information was found in the available literature on treatment technologies capable of effectively removing glyphosate from contaminated water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

HEXAZINONE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

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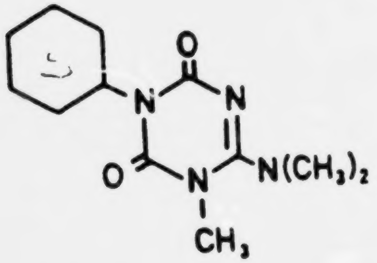
II. GENERAL INFORMATION AND PROPERTIES

CAS No.: 51235-04-2

Structural Formula:



3-Cyclohexyl-6-(dimethylamino)-1 methyl-1,3,5-triazine-2,4(1H,3H)-dione;

Synonyms

- ° Velpar; Hexazinone.

Use

- ° Contact and residual herbicide (Meister, 1983).
- ° Usage areas include plantations of coniferous trees, railroad right-of-ways, utilities, pipelines, petroleum tanks, drainage ditches, and sugar and alfalfa (Kennedy, 1984).

Properties (Kennedy, 1984; CHEMLAB, 1985)

Chemical Formula	$C_{11}H_{20}SO_2N_3$
Molecular Weight	252
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	115-117°C
Density	--
Vapor Pressure (86°C)	2×10^{-7} mm Hg
Specific Gravity	--
Water Solubility (25°C)	33,000 mg/L
Log Octanol/Water Partition Coefficient	-4.40 (calculated)
Taste Threshold	--
Odor Threshold	odorless
Conversion Factor	--

Occurrence

- ° Hexazinone has not been found in any surface or ground water samples analyzed from 9 samples taken at 2 locations or 6 samples from 6 locations, respectively (STORET, 1988).

Environmental Fate

- Hexazinone did not hydrolyze in water within the pH range of 5.7 to 9 during a period of 8 weeks (Rhodes, 1975a).

- In a soil aerobic metabolism study, hexazinone was added to a Fallsington sandy loam and a Flanagan silt loam at 4 ppm. ^{14}C-Hexazinone residues had a half-life of about 25 weeks. Of the extractable ^{14}C residues, half was present as parent compound and/or 3-cyclohexyl-1-methyl-6-methylamino-1,3,5-triazine-2,4-(1H,3H)-dione. Also present were 3-(4-hydroxycyclohexyl)-6-(dimethylamino)-1-methyl-1-(1H,3H)-dione and the triazine trione (Rhodes, 1975b).

- A soil column leaching study used ^{14}C-hexazinone, half of which was aged for 30 days and applied to Flanagan silt loam and Fallsington sandy loam. Leaching with a total of 20 inches of water showed that unaged hexazinone leached in the soils; however, leaching rates were slower for the aged samples, indicating that the degradation products may have less potential for contaminating ground water (Rhodes, 1975b).

- A field soil leaching study indicated that ^{14}C-hexazinone residues were leached into the lower sampling depths with increasing rainfall. A Keyport silt loam (2.75% organic matter; pH 6.5) and a Flanagan silt loam (4.02% organic matter; pH 5.0) were used. For the Keyport silt loam, ^{14}C residues were found at all depths measured, including the 8- to 12-inch depth, when total rainfall equaled 8.43 inches, 1 month after application of hexazinone. For the Flanagan silt loam, ^{14}C residues were found at all depths sampled, including the 12- to 15-inch depth, 1 month after application, when a total of 7.04 inches of rain had fallen (Rhodes, 1975c).

- A soil TLC test for Fallsington sandy loam and Flanagan silt loam gave R_f values for hexazinone of 0.85 and 0.68, respectively. This places hexazinone in Class 4, indicating it is very mobile in these soils (Rhodes, 1975c).

- In a terrestrial field dissipation study using a Keyport silt loam in Delaware, hexazinone had a half-life of less than 1 month. In a field study in Illinois (Flanagan silt loam), hexazinone had a half-life of more than 1 month (62% of the parent compound remained at 1 month) (Rhodes, 1975b). In a separate study with Keyport silt loam, some leaching of the parent compound to a depth of 12 to 18 inches was observed (Holt, 1979).

III. PHARMACOKINETICS

Absorption

- Rapisarda (1982) reported that a dose of 14 mg/kg ^{14}C-labeled hexazinone (>99% pure) was about 80% absorbed in 3 to 6 days (77% recovery in urine, 20% in feces) when administered by gastric intubation to male and female Charles River CD rats with or without 3 weeks of dietary preconditioning with unlabeled hexazinone.

- Rhodes et al. (1978) administered 2,500 ppm (125 mg/kg) hexazinone in the diet to male rats for 17 days. This was followed by a single dose of 18.3 mg/300 g (61 mg/kg) ^{14}C-labeled hexazinone. The hexazinone was rapidly absorbed within 72 hours, with 61% detected in the urine and 32% in the feces. Trace amounts were found in the gastrointestinal (GI) tract (0.6%, tissues not specified) and expired air (0.08%).

Distribution

- Orally administered hexazinone has not been demonstrated to accumulate preferentially in any tissue (Rhodes et al., 1978; Holt et al., 1979; Rapisarda, 1982).

- Studies in rats by Rapisarda (1982) and Rhodes et al. (1978) showed that no detectable levels of ^{14}C-hexazinone were found in any body tissues when the animals were administered >14 mg/kg hexazinone by gastric intubation with or without dietary preconditioning.

- In a study with dairy cows by Holt et al. (1979) hexazinone was given in the diet at 0, 1, 5 or 25 ppm for 30 days. Assuming that 1 ppm in the diet of a cow equals 0.015 mg/kg (Lehman, 1959), these levels correspond to 0, 0.015, 0.075 or 0.37 mg/kg/day. The investigators reported no detectable residues in milk, fat, liver, kidney or lean muscle.

Metabolism

- Major urinary metabolites of hexazinone in rats identified by Rhodes et al. (1978) were 3-(4-hydroxycyclohexyl)-6-(dimethylamino)1-methyl-1,3,5-triazine-2,4-(1H,3H)-dione (metabolite A); 3-cyclohexyl-6-(methylamino)-1-methyl-1,3,5-triazine-2,4-(1H, 3H)-dione (metabolite B); and 3-(4-hydroxycyclohexyl)-6-(methylamino)-1-methyl-1,3,5-triazine-2,4-(1H,3H)-dione (metabolite C). The percentages of these metabolites detected in the urine were 46.8, 11.5 and 39.3%, respectively. The major fecal metabolites detected by Rhodes et al. (1978) were A (26.3%) and C (55.2%). Less than 1% unchanged hexazinone was detected in the urine or the feces. Similar results were reported by Rapisarda (1982).

Excretion

- Rapisarda (1982) and Rhodes et al. (1978) reported that excretion of ^{14}C-hexazinone and/or its metabolites occurs mostly in the urine (61 to 77%) and in the feces (20 to 32%).

IV. HEALTH EFFECTS

Humans

- The Pesticide Incident Monitoring System data base (U.S. EPA, 1981) indicated that 3 of 43,729 incident reports involved hexazinone. Only one report cited exposure to hexazinone alone, without other compounds involved. A 26-year-old woman inhaled hexazinone dust (concentration not specified). Vomiting occurred within 24 hours. No other effects were reported and no treatment was administered. The other two reports did not involve human exposure.

Animals

Short-term Exposure

- Reported oral LD_{50} values for technical-grade hexazinone in rats range from 1,690 to >7,500 mg/kg (Matarese, 1977; Dashiell and Hinckle, 1980; Kennedy, 1984).

- Henry (1975) and Kennedy (1984) reported the oral LD_{50} value of technical-grade hexazinone in beagle dogs to be >3,400 mg/kg.

- Reported oral LD_{50} values for hexazinone in guinea pigs range from 800 to 860 mg/kg (Dale, 1973; Kennedy, 1984).

- Kennedy (1984) studied the response of male rats to repeated oral doses of hexazinone (89 or 98% active ingredient). Groups of six rats were intubated with hexazinone, 0 or 300 mg/kg, as a 5% suspension in corn oil. Animals were dosed 5 days/week for 2 weeks (10 total doses). Clinical signs and body weights were monitored daily. At 4 hours to 14 days after exposure to the last dose, microscopic evaluation of lung, trachea, liver, kidney, heart, testes, thymus, spleen, thyroid, GI tract, brain, and bone marrow was conducted. No gross or histological changes were noted in animals exposed to either active ingredient percentage of hexazinone.

- In an 8-week range-finding study (Kennedy and Kaplan, 1984), Charles River CD-1 mice (10/sex/dose) received hexazinone (>98% pure) in the diet for 8 consecutive weeks at concentrations of 0, 250, 500, 1,250, 2,500 or 10,000 ppm. Assuming 1 ppm in the diet of mice equals 0.15 mg/kg (Lehman, 1959), these dietary concentrations correspond to doses of about 0, 37.5, 75.0, 187.5, 375.0 or 1,500 mg/kg/day. No differences were observed in general behavior and appearance, mortality, body weights, food consumption or calculated food efficiency between control and exposed groups. No gross pathologic lesions were detected at necropsy. The only dose-related effects observed were increases in both absolute and relative liver weights in mice fed 10,000 ppm. A No-Observed-Adverse-Effect Level (NOAEL) of 2,500 ppm (375.0 mg/kg/day) was identified by the authors.

Dermal/Ocular Effects

- In an acute dermal toxicity test performed by McAlack (1976), up to 7,500 mg/kg of a 24% aqueous solution of hexazinone (reported to be 1,875 mg/kg of active ingredient) was applied occlusively for 24 hours to the shaved backs and trunks of male albino rabbits. No deaths were observed throughout a 14-day observation period. No other symptoms were reported.

- Morrow (1973) reported an acute dermal toxicity test in which 60 mL of a 24% aqueous solution of hexazinone (reported as 5,278 mg/kg) was applied occlusively to the shaved trunks of male albino rabbits for 24 hours. No mortalities were observed through an unspecified observation period. One animal exhibited a mild, transient skin irritation.

- In a 10-day study conducted by Kennedy (1984), semiocclusive dermal application of hexazinone for 6 hours/day for 10 days to male rabbits at 70 or 680 mg/kg/day resulted in no signs of skin irritation or toxicity. A trend toward elevated serum alkaline phosphatase (SAP) and serum glutamic pyruvic-transaminase (SGPT) activities was observed, but no hepatic damage was seen by microscopic evaluation. In a second 10-day study using 35, 150 or 770 mg/kg/day, the highest dose again resulted in elevated SAP and SGPT activities, but they returned to normal after 53 days of recovery. Histopathological evaluations were not performed in the second study.

- Edwards (1977) applied 6,000 mg/kg hexazinone as a 63% solution occlusively to the shaved backs and trunks of male albino rabbits. All rabbits showed moderate skin irritation which cleared 7 days after cessation of treatment. No treatment-related mortalities were reported after a 14-day observation period.

- Morrow (1972) reported the results of dermal irritation tests in which a single dose of 25 or 50% hexazinone was applied to the shaved, intact shoulder skin of each of 10 male guinea pigs. To test for sensitization, four sacral intradermal injections of 0.1 mL of a 15% solution were first given over a 3-week period. After a 2-week rest period, the guinea pigs were challenged with 25 or 50% hexazinone applied to the shaved, intact shoulder skin. The test material was found to be nonirritating and nonsensitizing at 48 hours post-application.

- Using a 10% solution, Goodman (1976) repeated the Morrow (1972) study with guinea pigs and observed no irritation or sensitization.

- Dashiell and Henry (1980) reported that in albino rabbits, a single dose of hexazinone applied as 27% (vehicle not specified) solution to one eye per animal and unwashed was a severe ocular irritant. When applied at 27% (vehicle not specified) and washed or at 4% (aqueous solution) unwashed, mild to moderate corneal cloudiness, iritis and/or conjunctivitis resulted. By 21 days post-treatment with the higher dose, two of the three rabbit eyes had returned to normal; a small area of mild corneal cloudiness persisted through the 35-day observation period in one of the three eyes. Eyes treated with lower doses were normal within 3 days.

Long-term Exposure

- In a 90-day feeding study, Sherman et al. (1973) fed beagle dogs (four/sex/dose) hexazinone (97.5% active ingredient) in the diet at levels of 0, 200, 1,000 or 5,000 ppm. Assuming 1 ppm in the diet of a dog equals 0.025 mg/kg/day (Lehman, 1959), these levels correspond to about 0, 5, 25 or 125 mg/kg/day. At the highest dose level tested, decreased food consumption, weight loss, elevated alkaline phosphatase activity, lowered albumin/globulin ratios and slightly elevated liver weights were noted. No gross or microscopic lesions were observed at necropsy. Based on the results of this study a NOAEL of 1,000 ppm (25 mg/kg/day) and a Lowest-Observed-Adverse-Effect Level (LOAEL) of 5,000 ppm (125 mg/kg/day) were identified.

- In a 90-day feeding study (Kennedy and Kaplan, 1984), Crl-CD rats (10/sex/dose) received hexazinone (>98% pure) at dietary levels of 0, 200, 1,000 or 5,000 ppm. Assuming 1 ppm in the diet of rats equals 0.05 mg/kg/day (Lehman, 1959), these levels correspond to about 0, 10, 50 or 250 mg/kg/day. Hematological and biochemical tests and urinalyses were conducted on subgroups of animals after 1, 2 or 3 months of feeding. Following 94 to 96 days of feeding, the rats were sacrificed and necropsied. The only statistically significant effect reported was a decrease in body weight in both males and females receiving 5,000 ppm. No differences in food consumption were reported. Results of histopathological examinations from the control and high-dose groups were unremarkable. The authors identified a NOAEL of 1,000 ppm (50 mg/kg/day).

- In a 1-year feeding study (Kaplan et al., 1975) weanling Charles River CD rats (36/sex/dose) received hexazinone (94 to 96% pure) at dietary levels of 0, 200, 1,000 or 2,500 ppm (which, according to the authors, corresponded to 0, 11, 60 or 160 mg/kg/day for males and 0, 14, 74 or 191 mg/kg/day for females). Results of this study indicated a decrease in weight gain by both sexes at 2,500 ppm and by females at 1,000 ppm. The authors indicated that various unspecified clinical, hematological and biochemical parameters revealed no evidence of adverse effects. No significant gross or histopathological changes attributable to hexazinone were noted. From the information presented in the study, a NOAEL of 200 ppm (11 mg/kg/day for males and 14 mg/kg/day for females) can be identified.

- In a 2-year study, Goldenthal and Trumball (1981) fed hexazinone (95 to 98% pure) to Charles River CD-1 mice (80/sex/dose) at dietary levels of 0, 200, 2,500 or 10,000 ppm. Assuming that 1 ppm in the diet of a mouse equals 0.15 mg/kg/day (Lehman, 1959), these levels correspond to 0, 30, 375 or 1,500 mg/kg/day. Corneal opacity, sloughing and discoloration of the distal tip of the tail were noted as early as the fourth week of the study in mice receiving 2,500 or 10,000 ppm. A statistically significant decrease in body weight was observed in male mice receiving 10,000 ppm and in female mice receiving 2,500 or 10,000 ppm. Statistically significant increases in liver weight were noted in male mice receiving 10,000 ppm; male and female mice in the 10,000-ppm dose group also displayed statistically significant increases in relative liver weight. Sporadic occurrence of statistically significant changes in hematological effects were considered by the authors to be unrelated to hexazinone treatment. Histologically, a number of liver changes were observed among mice fed 2,500 or 10,000 ppm. The most characteristic finding was hypertrophy of centrilobular parenchymal cells. Other histological changes included an increased incidence of hyperplastic liver nodules and an increased incidence and severity of liver cell necrosis. Mice fed 200 ppm showed no compound-related histopathological changes. A NOAEL of 200 ppm (30 mg/kg/day) was identified by the authors.

° Kennedy and Kaplan (1984) presented the results of a 2-year feeding study in which Crl-CD rats (36/sex/dose) received hexazinone (94 to 96% pure) at dietary levels of 0 (two groups), 200, 1,000 or 2,500 ppm (approximately 0, 10, 50 or 125 mg/kg/day assuming that 1 ppm in the diet of a rat equals 0.05 mg/kg/day)(Lehman, 1959). After 2 years of continuous feeding, all rats in all groups were sacrificed and examined. Males fed 2,500 ppm and females fed either 1,000 or 2,500 ppm had significantly lower body weights than controls ($p < 0.05$). Male rats fed 2,500 ppm had slightly elevated leukocyte counts with a greater proportion of eosinophils. Male rats fed either 1,000 or 2,500 ppm displayed decreased alkaline phosphatase activity. Statistically significant effects on organ weights included elevated relative lung weights in males fed 1,000 ppm; lower kidney and lower relative liver and heart weights in males fed 2,500 ppm; increased liver and spleen weights in females fed 200 ppm; and elevated stomach and relative brain weights in females fed 2,500 ppm. At necropsy, gross pathologic findings were similar among all groups. Changes attributed to hexazinone were not apparent in any of the tissues evaluated microscopically. The authors identified 200 ppm (10 mg/kg/day) as the NOAEL. However, the increased liver and spleen weights observed in females would indicate that 200 ppm might be more appropriately identified as a LOAEL.

Reproductive Effects

° In a one-generation reproduction study (Kennedy and Kaplan, 1984), Crl-CD rats (10/sex/dose) received hexazinone (>98% pure) for approximately 90 days at dietary levels of 0, 200, 1,000 or 5,000 ppm. Assuming that 1 ppm in the diet of rats equals 0.05 mg/kg/day (Lehman, 1959), this corresponds to approximately 0, 10, 50 and 250 mg/kg/day. Following the 90-day feeding period, six rats/sex/dose were selected to serve as the parental generation. The authors concluded that the rats had normal fertility. The young were delivered in normal numbers, and survival during the lactation period was unaffected. In the 5,000 ppm group, weights of pups at weaning (21 days) were significantly ($p < 0.01$) lower than controls or other test groups. The results of this study identify a NOAEL of 1,000 ppm (50 mg/kg/day) (no decrease in weanling weight).

° In a three-generation reproduction study (DuPont, 1979), Crl-CD rats (36/sex/dose) received hexazinone (98% pure) at dietary levels of 0, 200, 1,000 or 2,500 ppm for 90 days (approximately 0, 10, 50 or 125 mg/kg/day, assuming the above dietary assumptions for a rat). Following 90 days of feeding, 20 rats/sex/dose were selected to serve as the parental (F_0) generation. Reproductive parameters tested included the number of matings, number of pregnancies and number of pups per litter. Pups were weighed at weaning, and one male and female were selected from each litter to serve as parental rats for the second generation. Similar procedures were used to produce a third generation; the same reproductive parameters were collected for the second and third generations. The authors stated that there were no significant differences between the control and treated groups with respect to the various calculated indices (fertility, gestation, viability and lactation). However, body weights at weaning of pups in the 2,500 ppm dose group were significantly ($p < 0.05$) lower than those of controls for the F_2 and F_3 litters. The results of this study identify a NOAEL of 1,000 ppm (50 mg/kg/day).

Developmental Effects

- Kennedy and Kaplan (1984) presented the results of a study in which Charles River Crl-CD rats (25 to 27/dose) received hexazinone (97.5% pure) at dietary concentrations of 0, 200, 1,000 or 5,000 ppm (approximately 0, 10, 50 or 250 mg/kg/day following the previously stated dietary assumptions for the rat) on days 6 through 15 of gestation. Rats were observed daily for clinical signs and were weighed on gestation days 6, 16 and 21. On day 21, all rats were sacrificed and ovaries and uterine horns were weighed and examined. The number and location of live fetuses, dead fetuses and resorption sites were noted. Fetuses from the 0 and 5,000 ppm dose groups were evaluated for developmental effects (gross, soft tissue or skeletal abnormalities). At sacrifice, no adverse effects were observed for the dams. No malformations were noted in the fetuses. However, pup weights in the high-dose group were significantly lower than in the controls. This study identified a NOAEL of 1,000 ppm (50 mg/kg/day).

- Kennedy and Kaplan (1984) presented the results of a study in which New Zealand white rabbits (14-17/dose) received hexazinone suspended in a 0.5% aqueous methyl cellulose vehicle by oral intubation on days 6 through 19 of gestation at levels of 0, 20, 50 or 125 mg/kg/day. Rabbits were observed daily and body weights were recorded throughout gestation. On day 29 of gestation, all rabbits were sacrificed, uteri were excised and weighed, and the number of live, dead and resorbed fetuses was recorded. Each fetus was examined externally and internally for gross, soft tissue and skeletal abnormalities. No clinical signs of maternal or fetal toxicity were observed. Pregnancy rates among all groups compared favorably. The numbers of corpora lutea and implantations per group were not significantly different. Resorptions and fetal viability, weight and length were also similar among all groups. Based on the information presented in this study, a minimum NOAEL of 125 mg/kg/day for maternal toxicity, fetal toxicity, and teratogenicity can be identified.

Mutagenicity

- The ability of hexazinone to induce unscheduled DNA synthesis was assayed by Ford (1983) in freshly isolated hepatocytes from the livers of 8-week-old male Charles River/Sprague-Dawley rats. Hexazinone was tested at half-log concentrations from 1×10^{-5} to 10.0 mM and at 30.0 mM. No unscheduled DNA synthesis was observed.

- Valachos et al. (1982) conducted an *in vitro* assay for chromosomal aberrations in Chinese hamster ovary cells. Hexazinone was found to be clastogenic without S-9 activation at concentrations of 15.85 mM (4.0 mg/mL) or 19.82 mM (5.0 mg/mL); no significant increases in clastogenic activity were seen at 1.58, 3.94 and 7.93 mM (0.4, 1.0 and 2.0 mg/mL). With S-9 activation, significant increases in aberrations were noted only at a concentration of 15.85 mM (4.0 mg/mL). Concentrations above these yielded no analyzable metaphase cells due to cytotoxicity.

- In a study designed to evaluate the clastogenic potential of hexazinone in rat bone marrow cells (Farrow et al., 1982), Sprague-Dawley CD rats (12/sex/dose) were given a single dose of 0, 100, 300 or 1,000 mg/kg of hexazinone by gavage (vehicle not reported). No statistically significant increases in the frequency of chromosomal aberrations were observed at any of the dose levels tested. The authors concluded that, under the conditions of this study, hexazinone was not clastogenic.

- Hexazinone was tested for mutagenicity in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 at concentrations up to 7,000 ug/plate. The compound was not found to be mutagenic, with or without S-9 activation (DuPont, 1979).

Carcinogenicity

- Goldenthal and Trumball (1981) fed hexazinone (98% pure) for 2 years to mice (80/sex/dose) in the diet at 0, 200, 2,500, or 10,000 ppm (0, 30, 375 or 1,500 mg/kg/day, based on Lehman [1959]). A number of liver changes were observed histologically at the 2,500- and 10,000-ppm level. These included hypertrophy of the centrilobular parenchymal cells, increased incidence of hyperplastic liver nodules and liver cell necrosis. The authors concluded that hexazinone was not carcinogenic to mice.

- No carcinogenic effects were observed in Crl-CD rats (36/sex/dose) given hexazinone (94 to 96% pure) in the diet at 0, 200, 1,000, or 2,500 ppm (0, 10, 50, or 125 mg/kg/day) for 2 years (Kennedy and Kaplan, 1984). The authors concluded that none of the tumors were attributable to hexazinone.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA for hexazinone. It is, therefore, recommended that the Longer-term HA value of 3 mg/L (calculated below) for a 10-kg child be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study reported by Kennedy and Kaplan (1984) in which pregnant rabbits (14-17/dose) received hexazinone by oral intubation at levels of 0, 20, 50 or 125 mg/kg/day on days 6 through 19 of gestation was considered to serve as the basis for deriving the Ten-day HA for a 10-kg child. Since no signs of maternal or fetal toxicity were observed in this study, a NOAEL of 125 mg/kg/day (the highest dose tested) was identified. The NOAEL from this study is greater than that identified in a 90-day rat feeding study (50 mg/kg; Kennedy and Kaplan, 1984). The LOAEL from the one-generation rat reproduction study was 250 mg/kg based on decreased weanling weight. Effects at doses between 50 and 250 mg/kg have not been reported for the rat. However, in a 90-day dog study, a LOAEL of 125 mg/kg was identified (Sherman et al., 1973). Therefore, the rabbit study was not selected to derive a Ten-day value. It is, therefore, recommended that the Longer-term HA value of 3 mg/L for the 10-kg child be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The 90-day feeding study in dogs (Sherman et al., 1973) has been selected to serve as the basis for determination of the Longer-term HA for hexazinone. In this study, dogs (4/sex/dose) received hexazinone in the diet at levels of 0, 200, 1,000 or 5,000 ppm (0, 5, 25, or 125 mg/kg/day) for 90 days. Decreased food consumption and body weight gain, elevated alkaline phosphatase activity, lowered albumin/globulin ratios and slightly elevated liver weights were observed at the highest dose. A NOAEL of 1,000 ppm (25 mg/kg/day) and a LOAEL of 5,000 ppm (125 mg/kg/day) were identified. This NOAEL is generally supported by a 90-day rat feeding study that reported a NOAEL of 50 mg/kg/day (Kennedy and Kaplan, 1984). Effects in dogs exposed to hexazinone at 50 mg/kg/day have not been reported.

Using a NOAEL of 25 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(25 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 2.5 \text{ mg/L } (3{,}000 \text{ ug/L})$$

where:

25 mg/kg/day = NOAEL, based on absence of hepatic effects or weight loss in dogs exposed to hexazinone via the diet for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(25 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 8.75 \text{ mg/L } (9{,}000 \text{ ug/L})$$

where:

25 mg/kg/day = NOAEL, based on absence of hepatic effects or weight loss in dogs exposed to hexazinone via the diet for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

A 2-year rat feeding/oncogenicity study (Kennedy and Kaplan, 1984) was selected as the basis for determination of the Lifetime HA for hexazinone. Crl-CD rats (36/sex/dose) received 0, 200, 1,000, or 2,500 ppm hexazinone (0, 10, 50, or 125 mg/kg/day) for 2 years. Body weight gain in males and females in the 2,500-ppm group, and females in the 1,000-ppm group, was significantly lower than that in controls. No clinical, hematological or urinary evidence of toxicity was reported. Based on decreased body weight gain, a NOAEL of 200 ppm (10 mg/kg/day) and LOAEL of 1,000 ppm (50 mg/kg/day) were identified.

Using a NOAEL of 10 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(10\ \text{mg/kg/day})}{(100)\ (3)} = 0.03\ \text{mg/kg/day}$$

where:

10 mg/kg/day = NOAEL, based on absence of body weight effects in rats exposed to hexazinone via the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = modifying factor; to account for data gaps (chronic dog-feeding study) in the total data base for hexazinone.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.03\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 1.05\ \text{mg/L}\ (1{,}000\ \text{ug/L})$$

where:

0.03 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of Lifetime Health Advisory

Lifetime HA = (1.05 mg/L) (20%) = 0.21 mg/L (200 ug/L)

where:

1.05 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenicity in rats or mice has been observed.
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of hexazinone.
- The criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), place hexazinone in Group D: not classified. This category is for substances with inadequate or no animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Residue tolerances range from 0.5 to 5.0 ppm for the combined residues of hexazinone and its metabolites in or on the raw agricultural commodities pineapple, pineapple fodder and forage (U.S. EPA, 1985a).

VII. ANALYTICAL METHODS

- Analysis of hexazinone is by a gas chromatographic method applicable to the determination of certain organonitrogen pesticides in water samples (U.S. EPA, 1985b). This method requires a solvent extraction of approximately 1 liter of sample with methylene chloride using a separatory funnel. The methylene chloride extract is dried and exchanged to acetone during concentration to a volume of 10 mL or less. The compounds in the extract are separated by gas chromatography, and measurement is made with a thermionic bead detector. The method detection limit for hexazinone is 0.72 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information was found in the available literature on treatment technologies used to remove hexazinone from contaminated water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

MALEIC HYDRAZIDE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

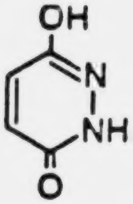
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 123-33-1

Structural Formula



1,2-Dihydro-3,6-pyridazinedione

Synonyms

- Antergon; Chemform; De-Sprout; MH; Retard; Slo-Gro; Sucker-Stuff; (Meister, 1983).

Uses

- Plant growth retardant (Meister, 1983).

Properties (Meister, 1983; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_4H_4O_2N_2$
Molecular Weight	112.09
Physical State (25°C)	Crystalline solid
Boiling Point	--
Melting Point	292°C
Density	1.60
Vapor Pressure (50°C)	0 mm Hg
Specific Gravity	--
Water Solubility (25°C)	6,000 mg/L
Log Octanol/Water Partition Coefficient	-3.67 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- No information was found in the available literature on the occurrence of maleic hydrazide.

Environmental Fate

- Salts of maleic hydrazide will dissociate in solutions above pH 4.5 and exist only as maleic hydrazide. Maleic hydrazide is stable to hydrolysis at pHs of 3, 6 and 9. Photolysis potential has not been addressed (Registration Standard Science Chapter for Maleic Hydrazide; WSSA, 1983).

- In field dissipation studies using various soils from the eastern, southern and midwestern U.S., the half-lives were reported to be between 14 and 100 days. There is no pattern, but the half-life may be related to organic matter content. Degradation by soil micro-organisms appears to be rapid (Registration Standard Science Chapter for Maleic Hydrazide; WSSA, 1983).

- There is some indication that maleic hydrazide is highly mobile in unaged soils. Aerobic aging of maleic hydrazide results in a lowering of leaching potential (Registration Standard Science Chapter for Maleic Hydrazide; WSSA, 1983).

III. PHARMACOKINETICS

Absorption

- Mays et al. (1968) administered single oral doses of ^{14}C-labeled maleic hydrazide to rats. After 6 days, only 12% had been excreted in the feces, suggesting that 88% had been absorbed.

Distribution

- Kennedy and Keplinger (1971) administered ^{14}C-labeled maleic hydrazide to pregnant rats in daily doses of either 0.5 or 5.0 mg/kg. Fetuses from dams sacrificed on day 20 were found to contain label equivalent to 20 to 35 ppb of the parent compound at the 0.5-mg/kg dose level, and 156 to 308 ppb at the 5.0-mg/kg dose level. Pups from females that were allowed to litter were sacrificed at 8 and at 24 hours, and stomach coagulum was analyzed to determine transfer through the milk. At the 0.5 mg/kg dose, the coagulum contained 4 to 7 ppb at 8 hours and 2 ppb at 24 hours; at the 5.0 mg/kg dose, the figures for 8 and 24 hours were 79 to 89 ppb and 7 to 8 ppb, respectively. These results suggest that maleic hydrazide crossed the placenta and was also transmitted to the pups via the milk.

Metabolism

- Barnes et al. (1957) reported that rabbits administered a single oral dose of 100 mg/kg of maleic hydrazide excreted 43 to 62% of the dose, unchanged, within 48 hours. The route of excretion (urinary or fecal) was not stated. The results were similar following a dose of 2,000 mg/kg, and no glucuronide or ethereal sulfate conjugates were found.

- Oral administration of maleic hydrazide labeled with ^{14}C to rats resulted in excretion of 0.2% labeled carbon dioxide in the expired air over a 6-day observation period (Mays et al., 1968). Urinary products (77% of the total dose) were largely unchanged maleic hydrazide (92 to 94% of the urinary total) and conjugates of maleic hydrazide (6 to 8%).

Excretion

- Mays et al. (1968) administered single oral doses of ^{14}C-maleic hydrazide to rats. Over a 6-day observation period, the animals excreted 0.2% of the label as carbon dioxide in the expired air, 12% in the feces and 77% in the urine. Only trace amounts were detected in tissues and blood after 3 days.

IV. HEALTH EFFECTS

Humans

- No information on human exposure to maleic hydrazide was found in the available literature.

Animals

Short-term Exposure

- The acute oral toxicity of maleic hydrazide (purity not specified) in rats was determined with administration of four dose levels to groups of five animals, with a 15-day observation period (Reagan and Becci, 1982). At dose levels of 5,000, 6,300, 7,940 or 10,000 mg/kg, deaths occurring in the male animals were 0/5, 0/5, 1/5 and 5/5, respectively, while those for female animals were 1/5, 1/5, 4/5 and 5/5, respectively. The LD_{50} values were calculated to be 6,300 mg/kg for males, 6,680 mg/kg for females and 7,500 mg/kg for both sexes combined. Adverse effects noted included ataxia, diarrhea, salivation, decreased motor activity and blood in the intestines and stomach.

- Sprague-Dawley rats (five males and five females) were fasted for 16 hours and then given a single oral dose of technical maleic hydrazide (purity not specified) at a level of 5,000 mg/kg and observed for 14 days (Shapiro, 1977a). No deaths occurred during this period. Necropsies were not performed, and no details were given with respect to adverse effects that may have been observed.

- The acute oral toxicity of the diethanolamine salt of maleic hydrazide (MH-DEA) (purity not specified) was determined in rats and rabbits (Uniroyal Chemical, 1971). In both species, MH-DEA was lethal at a level of 1,000 mg/kg, while doses between 300 and 500 mg/kg showed no toxicity in either species. The LD_{50} value for both species was calculated to be 700 mg/kg.

- Rats were used for a comparison of the acute oral toxicity of the sodium and diethanolamine salts (purities not specified) of maleic hydrazide (Tate, 1951). The diethanolamine salt showed an LD_{50} value of 2,350 mg/kg, while the LD_{50} for the sodium salt (MH-Na) was 6,950 mg/kg. No details of the study were given.

- The acute oral LD_{50} value of technical-grade maleic hydrazide (purity not specified) for rabbits was greater than 4,000 mg/kg (Lehman, 1951). No details of the study were available.

Dermal/Ocular Effects

- Technical-grade maleic hydrazide was tested on male and female New Zealand rabbits for both skin and eye irritation (Shapiro, 1977b,c). Applied at 0.5 mL, the maleic hydrazide was scored as a mild primary skin irritant. In the eye test, 100 mg of the material was used, and maleic hydrazide was judged not to be an eye irritant.

- The acute dermal toxicity of maleic hydrazide (purity and form not specified) was determined in five male and five female New Zealand rabbits (Shapiro, 1977d). The skin of two males and three females was abraded. A single dose of 20,000 mg/kg was applied, and the animals were observed for 14 days. On the first day, two males (one with abraded skin) and one female died. The animals that died exhibited ataxia, shallow respiration and were comatose.

- In an evaluation of the acute dermal toxicity of Royal MH-30 (30% MH-DEA) and maleic hydrazide-technical, both formulations were stated to be mild primary skin irritants and slight eye irritants (Uniroyal Chemical, 1977). Individual details of the study were not given.

Long-term Exposure

- Rats were fed MH-Na or MH-DEA (purity not specified) in the diet for 11 weeks (Tate, 1951). The MH-Na was given at dose levels of 0.5% or 5.0% (5,000 or 50,000 ppm). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to 250 or 2,500 mg/kg/day. No significant mortality or other adverse effects were noted (no details given). The No-Observed-Adverse-Effect Level (NOAEL) for MH-Na in this study is 2,500 mg/kg (the highest dose tested). The MH-DEA was fed at a level of 0.1% (1,000 ppm) for 11 weeks. This is equivalent to a dose of 50 mg/kg/day (Lehman, 1959). At the end of 11 weeks, 21/24 animals had died. The author stated that after further investigation (details not given), it was concluded that the observed mortality was due to the DEA component of the formulation.

- The toxicity of maleic hydrazide in the diet for 1 year (320 to 360 days) was investigated in rats and dogs (Mukhorina, 1962). Rats received oral doses of maleic hydrazide at 0.7, 1.5 or 3 mg/kg/day, and a fourth group received 7 mg/kg MH-DEA. Dogs were administered an oral dose of 0.7 mg/kg/day maleic hydrazide. Other details in this translation on study design and conduct were not clear. Rats exposed at the high dose had hyperemia and hemorrhage of the lungs, myocardium, liver and brain, abnormal glucose-tolerance curves, lowered liver glycogen, dystrophic changes in the liver, nephritis, interstitial pneumonia, loss of hair and significant reduction in weight gain compared with the controls (at 4 months, controls had gained 30%; those fed maleic hydrazide at 3 mg/kg/day had gained only 21%). Dogs fed 0.7 mg/kg/day maleic hydrazide showed no significant adverse changes, and it appears that for both the rat and the dog the level of 0.7 mg/kg/day MH-DEA was a NOAEL.

- Mukhorina (1962) also reported on a study done in mongrel mice given 0.7 mg/kg/day maleic hydrazide (purity not specified) in the diet for 320 to 360 days. No pathological changes were found. Based on these data, the NOAEL for MH-DEA in the mouse is 0.7 mg/kg/day.

- In a study by Food Research Labs (1954), MH-Na was fed in the diet to rats (number not specified) from weaning for two years. Levels of MH-Na (expressed as the free acid) were 0.0, 0.5, 1.0, 2.0 or 5.0% (0, 5,000, 10,000, 20,000 or 50,000 ppm). Assuming that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this is equivalent to doses of 0, 250, 500, 1,000 or 2,500 mg/kg/day. There were no changes in blood or urine and no dose- or time-dependent effects on longevity. Other study details were not presented. Based on these observations, the NOAEL identified from this study is 2,500 mg/kg/day (highest dose tested) for the rat.

- In a similar study in dogs (Food Research Labs, 1954) animals were fed doses of 0.0, 0.6, 1.2 or 2.4% maleic hydrazide (as MH-Na) in the diet for 1 year. Assuming 1% (10,000 ppm) in the diet of dogs corresponds to 250 mg/kg/day (Lehman, 1959), this is equivalent to a dose of 500 mg/kg/day. No effects attributable to exposure were detected.

- Van Der Heijden et al. (1981) fed technical maleic hydrazide, 99% active ingredient (a.i.) and containing less than 1.5 mg hydrazine/kg as an impurity to rats at dietary levels of 1.0 or 2.0% (10,000 or 20,000 ppm) for 28 months. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 500 or 1,000 mg/kg/day. These two levels of maleic hydrazide in the diet caused proteinuria and increased the protein/creatinine ratio in the urine of both sexes, although there were no detectable histopathological changes in the kidney or the urinary tract. Based on the effects on kidney function, the no-effect level was considered by the authors to be lower than 1.0% maleic hydrazide in the diet of rats. On this basis, a Lowest-Observed-Adverse-Effect Level (LOAEL) of 500 mg/kg is identified.

Reproductive Effects

- In a two-generation reproduction study by Kehoe and MacKenzie (1983), Charles River CD(SD)BR rats (15 males and 30 females/dose) were administered the potassium salt of maleic hydrazide (K-MH) (purity not specified) at dietary concentrations of 0, 1,000, 10,000 or 30,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to 0, 50, 500 and 1,500 mg/kg/day. No adverse effects on reproductive indices were observed at any dietary level. However, increased mortality was observed in F_1 parents that received 30,000 ppm. Also at this dose level, body weights were reduced in F_0 parents during growth and reproduction and in F_1 and F_2 pups during lactation. Based on the postnatal decrease in the body weight of pups, a reproductive NOAEL of 10,000 ppm (500 mg/kg/day) is identified.

- In a four-generation reproduction study in rats (Food Research Labs, 1954), animals were fed MH-Na (purity not specified) in the diet at dose levels of 0.5, 1.0, 2.0 or 5.0% (5,000, 10,000, 20,000 or 50,000 ppm) (expressed in terms of free acid). Assuming 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this is equivalent to 250, 500, 1,000 or 2,500 mg/kg/day. The authors reported that there were no effects on fertility, lactation or other reproductive parameters, but no data from the study were presented for an adequate assessment of these findings.

Developmental Effects

- Khera et al. (1979) administered maleic hydrazide (97% purity) to pregnant rats by gavage on days 6 to 15 of gestation at doses of 0, 400, 800, 1,200 or 1,600 mg/kg/day. Animals were sacrificed on day 22. No sign of toxicity or adverse effect on maternal weight gain was observed at any dose level tested. Values for corpora lutea, total implants, resorptions, dead fetuses, male/female ratio and fetal weight were within the control range. The number of live fetuses was decreased at the 1,200-mg/kg dose, but this was not statistically significant and did not occur at the highest dose tested. Fetuses examined for external, soft-tissue and skeletal abnormalities showed no increase in frequency of abnormalities at any dose level tested. Based on the results of this study, a NOAEL of 1,600 mg/kg/day (the highest dose tested) is identified for maternal effects, fetotoxicity and teratogenic effects.

- Hansen et al. (1984) studied the teratogenic effects of MH-Na and the monoethanolamine salt (MH-MEA) on fetuses from female rats exposed by gavage to doses of 500, 1,500 or 3,000 mg/kg/day in the diet at various stages of gestation. Replicate tests were run. No increased frequency of gross, skeletal or visceral abnormalities was observed in animals dosed by gavage on days 6 to 15 of gestation with 500 mg/kg/day of either MH-Na or MH-MEA. An increased frequency of minor skeletal variants (asymmetrical and bipartite sternebrae, wavy ribs, fused ribs, rudiment of cervical rib, single bipartite or other variations in thoracic vertebrae) was observed in animals receiving 1,500 ($p < 0.01$) or 3,000 ($p < 0.1$) mg/kg/day of MH-MEA on days 6 to 15, but this was observed neither in animals exposed to 3,000 mg/kg/day for days 1 to 21 of gestation nor in a replicate experiment. Similarly, MH-Na produced marginal increases in minor skeletal variants in one experiment at doses of 1,500 mg/kg/day for days 6 to 15 ($p < 0.1$) or 3,000 mg/kg/day for days 1 to 21 ($p < 0.1$), but this was not observed in a replicate experiment. Rats dosed with 3,000 mg/kg/day MH-MEA in the diet exhibited a significant decrease in maternal body weight and in weight gain compared to the controls. This effect was not observed when 3,000 mg/kg was given on days 1 to 21 by gavage, and there was no significant effect on food intake. Exposure to 3,000 mg/kg in the diet caused a significant increase in resorptions ($p < 0.001$) and a decrease in mean fetal weight ($p < 0.001$). Similar but less pronounced effects were observed when this dose was given by gavage. In addition, postimplantation loss was increased significantly ($p < 0.01$) in both experiments. The authors theorized that the more severe effects observed when the MH-MEA was fed in the diet (versus gavage) could be due to an alteration in the palatability of the diet, resulting in decreased food consumption. In contrast to the results with MH-MEA, MH-Na had no adverse effects on the dams except for a reduction in food consumption for days 1 to 6 in the group exposed from days 1 to 21 at 3,000 mg/kg. There were significant differences in body weight of the pups (up to age 35 days) of dams administered MH-MEA by gavage at 3,000 mg/kg/day from day 6 of gestation through day 21 of lactation; a significant delay in the pups' startle response to an auditory stimulus, significantly higher brain weight in both male and female pups, and a delay in unfolding of the pinna were noted also. The authors attributed the increase in relative brain weight to the lower body weight. The delay in the startle response in MH-MEA dosed offspring was considered the most significant effect, since it was observed in both sexes, but the authors noted that it cannot be explained. Based on these data, maternal, fetotoxic and teratogenic NOAELs of 1,500, 1,500 and 500 mg/kg/day, respectively, were identified for both MH-MEA and MH-Na.

- Aldridge (1983, cited in U.S. EPA, 1985a) administered K-MH by gavage at doses of 0, 100, 300 or 1,000 mg/kg/day to Dutch Belted rabbits (16/dose) on days 7 through 27 of gestation. No signs of maternal toxicity were reported, and the NOAEL for this effect is identified as 1,000 mg/kg/day (the highest dose tested). Malformed scapulae were observed in fetuses from the 300- and 1,000-mg/kg/day dose groups. An evaluation of this study by the Office of Pesticide Programs (U.S. EPA, 1985a) concluded that scapular malformations are rare and considered to be a major skeletal defect. Historical data for Dutch Belted rabbits from the testing laboratory (IRDC) indicated that scapular anomalies were observed in only 1 of 1,586 fetuses examined from 264 litters. Based on this information, a NOAEL of 100 mg/kg/day is identified for developmental effects.

Mutagenicity

- The mutagenic activity of maleic hydrazide and its formulations has been investigated in a number of laboratories. These studies are complicated by the fact that hydrazine (a powerful mutagen) is a common contaminant of these preparations, and N-nitrosoethanolamine (also a mutagen) may be present in MH-DEA. Present data are inadequate to determine with certainty whether any mutagenic activity of maleic hydrazide is due to impurities and not the maleic hydrazide itself.

- Tosk et al. (1979) reported that maleic hydrazide (purity not specified), at levels of 5, 10 and 20 mg, was not mutagenic in *Salmonella typhimurium* (TA 1530). However, two formulations (MH-30 and Royal MH), at 50, 100 and 200 uL (undiluted), were highly mutagenic in this system.

- Moriya et al. (1983) reported that maleic hydrazide was not mutagenic in five strains of *S. typhimurium*.

- Ercegovich and Rashid (1977) observed a weak mutagenic response with maleic hydrazide (purity not specified) in five strains of S. typhimurium.

- Shiau et al. (1980) reported that maleic hydrazide was mutagenic, with and without activation, in several Bacillus subtilis strains.

- Epstein et al. (1972) reported that maleic hydrazide (500 mg/kg) was not mutagenic in a dominant-lethal assay in the mouse.

- Nasrat (1965) reported a slight increase in the frequency of sex-linked recessive lethals in the progeny of Drosophila melanogaster males reared on food containing 0.4% maleic hydrazide.

- Manna (1971) indicated that exposure to a 5% aqueous solution of maleic hydrazide produced chromosomal aberrations in the bone marrow of mice in a manner similar to that produced by x-rays and other known mutagens.

- Chaubey et al. (1978) reported that intraperitoneal injection of 100 or 200 mg/kg maleic hyerazide (purity not specified) did not affect the incidence of bone marrow erythrocyte micronuclei or the ratio of poly- to normochromatic erythrocytes in male Swiss mice.

- Sabharwal and Lockhard (1980) reported that at concentrations above 100 ppm, maleic hydrazide induced dose-related increases in sister chromated exchange (SCE) in human lymphocytes and V79 Chinese hamster cells. Commercial formulations of maleic hydrazide (Royal MH and MH-30) at the 250- and 500-mg/kg doses did not cause an increase in micronucleated polychromatic erythrocytes in a mouse micronucleus test.

- Stetka and Wolff (1976) reported that maleic hydrazide (11 and 112 mg/L; purity not specified) caused no significant effect in an SCE assay.

- Nishi et al. (1979) reported that maleic hydrazide (1,000 ug/L; purity not specified), MH-DEA (20,000 ug/mL) and MH-K (20,000 ug/mL) produced cytogenetic effects in Chinese hamster V79 cells in vitro.

- Paschin (1981) reported that in the concentration range of 1,800 to 2,500 mg/L maleic hydrazide (purity not specified) was mutagenic for the thymidine kinase locus of mouse lymphoma cells.

Carcinogenicity

- The carcinogenicity of maleic hydrazide (purity not specified) was evaluated in two hybrid strains of mice (C57BL/6 x AKR and C57BL/6 x C3H/Anf) (Kotin et al., 1968; Innes et al., 1969). Beginning at 7 days of age, mice were given maleic hydrazide at 1,000 mg/kg/day (suspended in 0.5% gelatin) by stomach tube. After 28 days of age, they were given maleic hydrazide in the diet at 3,000 ppm for 18 months. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to a dose of 450 mg/kg/day. These were the maximum tolerated doses. No evidence of increased tumor frequency was detected in gross or histologic examination.

- Barnes et al. (1957) fed maleic hydrazide at a level of 1% (10,000 ppm) in the diet of rats and mice (10 to 15/sex/dose) for a total of 100 weeks. Assuming that 1 ppm in the diet corresponds to 0.05 mg/kg/day in rats and 0.15 mg/kg/day in mice (Lehman, 1959), this is equivalent to a dose of 500 mg/kg/day in rats and 1,500 mg/kg/day in mice. A concurrent study was conducted in which the maleic hydrazide (500 mg/kg/week, corresponding to 71 mg/kg/day) was injected subcutaneously (sc) for the same length of time. No increase in the incidence of tumors was observed in animals exposed by either route when compared with controls (data were pooled).

- Cabral and Ponomarkov (1982) administered maleic hydrazide by gavage in weekly doses of 510 mg/kg in 0.2 mL olive oil to male and female C57BL/B6 mice for 120 weeks. Controls received 0.2 mL olive oil alone, and a third group served as untreated controls. A simultaneous study was conducted using sc injection as the route of administration. There was no evidence of carcinogenicity in the study.

- Van Der Heijden et al. (1981) fed maleic hydrazide (99% pure) containing less than 1.5 mg hydrazine/kg as impurity to rats at dietary levels of 1.0 or 2.0% (10,000 or 20,000 ppm) for 28 months. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 500 or 1,000 mg/kg/day. Histological examination revealed no increase in the tumor incidence in exposed animals compared with the control group.

- In a study by Uniroyal Chemical (1971), mice were administered maleic hydrazide (0.5% in water) by gavage twice weekly beginning at 2 months of age (weight 15 to 18 g) for a total of 2 years. A parallel study was conducted using sc administration. No carcinogenic effect was reported, but specific details of the study were not presented.

- Uniroyal Chemical (1971) reported a 2-year study in Wistar-derived rats in which MH-Na was included in the diet at levels of 0, 0.5, 1,0, 2.0 or 5.0% (0, 5,000, 10,000, 20,000 or 50,000 ppm). Assuming that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this is equivalent to doses of 0, 250, 500, 1,000 or 2,500 mg/kg/day. Although no experimental details were presented, it was concluded that the MH-Na resulted in no blood dyscrasias or tissue pathology, and no indication of carcinogenic potential was detected.

- Epstein and Mantel (1968) used random-bred infant Swiss mice (ICR/Ha) to assess the carcinogenic effects of maleic hydrazide when administered during the neonatal period. The free acid form of maleic hydrazide (containing 0.4% hydrazine impurity) was prepared as an aqueous solution of 5 mg/mL, or as a suspension in redistilled tricaprylin at a concentration of 50 mg/mL. The mice were given injections in the nape of the neck on days 1, 7, 14 and 21 following birth. Six litters received the maleic hydrazide aqueous solution (total dose: 3 mg), and 16 litters received the maleic hydrazide suspension (total dose: 55 mg). One litter received one injection of the suspension at a higher dose (100 mg/mL, total dose: 10 mg), but this was lethal to all mice. A total of 16 litters served as controls (treated with solvents alone). The experiment was terminated between 49 and 51 weeks. The mice that received a total dose of 55 mg in the 3-week period had a high incidence of hepatomas: 65% of 26 male mice alive at 49 weeks, in contrast to solvent controls in which hepatomas occurred in 8% of 48 male mice. The males that received 3 mg total had an 18% incidence of hepatomas. In addition to these lesions, hepatic "atypia" was observed in five males (at 55 mg) and eight females, which the authors judged might be preneoplastic. At the 3-mg level, one atypia was seen in each sex. It was concluded that maleic hydrazide was highly carcinogenic in the male mice. The authors also noted that since there was a complete absence of multiple pulmonary adenomas and pulmonary carcinomas, it was unlikely that the carcinogenicity of maleic hydrazide was due to hydrazine (either present as trace contamination or formed by metabolism), since hydrazine is a potent lung carcinogen in several species of rats and mice (including CBA mice).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\underline{\quad}\ \text{L/day})} = \underline{\quad}\ \text{mg/L}\ (\underline{\quad}\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

____ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

Several studies (Tate, 1951; Mukhorina, 1962; Hansen et al., 1984) indicate that the DEA ion is toxic and may contribute to the toxicity of the MH-DEA salt. For this reason, studies involving MH-DEA have not been considered as candidates in calculating HA values for maleic hydrazide.

One-day Health Advisory

No information was found in the available literature that was suitable for deriving a One-day HA value for maleic hydrazide. It is, therefore, recommended that the Ten-day HA value for a 10-kg child (10 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The developmental toxicity study by Aldridge (1983, cited in U.S. EPA, 1985a) has been selected to serve as the basis for the Ten-day HA. In this study, the potassium salt of maleic hydrazide (K-MH) was administered by gavage at doses of 0, 100, 300 or 1,000 mg/kg/day to Dutch Belted rabbits (16/dose) on days 7 through 27 of gestation. Malformed scapulae were observed in fetuses from the 300- and 1,000-mg/kg/day dose groups. Although the incidence of these malformations was not statistically significant and did not occur in a dose-related fashion, malformed scapulae are a rare, major skeletal defect. Additionally, historical data for this breed of rabbits indicate that scapular anomalies were observed in only 1 of 1,586 fetuses examined from 264 litters. For these reasons U.S. EPA (1985a) concluded that the possibility of teratogenic activity at these dose levels cannot be ruled out. The NOAEL for teratogenic effects is identified as 100 mg/kg/day.

Although a teratogenic response is clearly a reasonable basis upon which to base an HA for an adult, there is some question about whether the Ten-day HA for a 10-kg child can be based upon such a study. However, a teratogenic study is of appropriate duration and does supply some information concerning fetotoxicity. Since the fetus may be more sensitive to the chemical than a 10-kg child and since a teratogenic study is of appropriate duration, it is judged that, though possibly overly conservative, it is reasonable in this case to base the Ten-day HA for a 10-kg child on a developmental toxicity study.

Using a NOAEL of 100 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(100\text{ mg/kg/day})\ (10\text{ kg})}{(100)\ (1\text{ L/day})} = 10\text{ mg/L } (10{,}000\text{ ug/L})$$

where:

100 mg/kg/day = NOAEL, based on the absence of teratogenic effects in rabbits exposed to K-MH by gavage on days 7 to 27 of gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

No studies were found that were adequate for calculation of Longer-term HA values for maleic hydrazide. An 11-week feeding study in rats by Tate (1951) identified a NOAEL of 2,500 mg/kg/day, and 2-year feeding studies in rats and dogs by Food Research Laboratories (1954) identified NOAEL values of 2,500 and 500 mg/kg/day, respectively. These studies have not been selected because they provided too little experimental detail to be suitable for calculation of an HA value. It is, therefore, recommended that the Drining Water Equivalent Level (DWEL) of 18 mg/L, calculated below, be used as a conservative estimate of the Longer-term HA for a 70-kg adult and that the modified DWEL of 5 mg/L (adjusted for a 10-kg child) be used as a conservative estimate of the Longer-term HA for a 10-kg child.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 28-month feeding study in rats by Van Der Heijden et al. (1981) has been selected to serve as the basis for the Lifetime HA value for maleic hydrazide. Based on proteinuria (in the absence of visible histological effects in kidney), a LOAEL of 500 mg/kg/day was identified. This is a conservative selection, since 2-year feeding studies in dogs and rats by Food Research Laboratories (1954) identified NOAEL values of 500 and 2,500 mg/kg/day, respectively; those studies were not selected, however, because few data or details were provided.

Using the LOAEL identified by Van Der Heijden et al. (1981), the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(500\ \text{mg/kg/day})}{(1{,}000)} = 0.5\ \text{mg/kg/day}$$

where:

500 mg/kg/day = LOAEL, based on proteinuria in rats exposed to maleic hydrazide in the diet for 28 months.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.5\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 17.5\ \text{mg/L}\ (18{,}000\ \text{ug/L})$$

where:

0.5 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (17.5\ \text{mg/L})\ (20\%) = 3.5\ \text{mg/L}\ (4{,}000\ \text{ug/L})$$

where:

17.5 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenic activity was detected in five studies in which maleic hydrazide was administered orally to mice or rats for periods from 18 to more than 2 years (Kotin et al., 1968; Innes et al., 1969; Barnes et al., 1957; Cabral and Ponomarkov, 1982; Van Der Heijden et al., 1981; Uniroyal Chemical, 1971). Increased incidence of hepatomas has been reported in mice exposed by sc injection during the first 3 weeks of life (Epstein and Mantel, 1968).

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of maleic hydrazide.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), maleic hydrazide may be classified in Group D: not classified. This group is used for substances with inadequate human or animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA (1985b) has established residue tolerances for maleic hydrazide in or on raw agricultural commodities that range from 15.0 to 50.0 ppm.

VII. ANALYTICAL METHODS

- There is no standardized method for the determination of maleic hydrazide in water samples. A procedure has been reported for the estimation of maleic hydrazide residues on various foods (U.S. FDA, 1975). In this procedure, the sample is boiled in alkaline solution to drive off volatile basic interferences. Distillation with zinc and nitrogen sweep expels hydrazine liberated from maleic hydrazide. Hydrazine is reacted in acid solution with p-dimethylaminobenzaldehyde to form a yellow compound which is measured spectrophotometrically.

VIII. TREATMENT TECHNOLOGIES

- Currently available treatment technologies have not been tested for their effectiveness in removing maleic hydrazide from drinking water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

MCPA
(4-Chloro-2-Methylphenoxy)-Acetic Acid

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

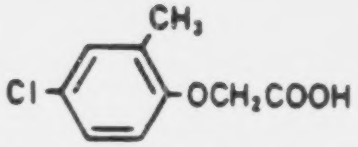
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 94-74-6

Structural Formula



(4-Chloro-2-methylphenoxy)-acetic acid

Synonyms

- MCPA; MCP; Agroxone; Hormotuho; Metaxon.

Uses

- MCPA is a hormone-type herbicide used to control annual and perennial weeds in cereals, grassland and turf (Hayes, 1982).

Properties (CHEMLAB, 1985; Meister, 1983)

Chemical Formula	$C_9H_9O_3Cl$
Molecular Weight	200.63
Physical State (25°C)	Light brown solid
Boiling Point	--
Melting Point	118 to 119°C
Vapor Pressure (25°C)	--
Density (25°C)	1.56
Water Solubility	825 mg/L (20° C)
Log Octanol/Water Partition Coefficient	2.07 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- MCPA has been found in 4 of 18 surface water samples analyzed and in none of 118 ground water samples (STORET, 1988). Samples were collected at 13 surface water locations and 117 ground water locations. MCPA was found only in California. The 85th percentile of all nonzero samples was 0.54 ug/L in surface water, and the range of concentrations was 0.04 to 0.54 ug/L. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- MCPA has been detected in groundwater in Montana. The highest level found was 5.5 ppb (5.5 ug/L).

- Frank et al. (1979) detected MCPA residues (1.1 to 1000 ppb) in 2 of 237 wells in Ontario, Canada, between 1969 and 1978.

Environmental Fate

- MCPA is not hydrolyzed at pH 7 and 34 to 35°C (Soderquist and Crosby, 1974, 1975). MCPA in aqueous solution (pH 8.3) has a photolytic half-life of 20 to 24 days in sunlight. With fluorescent light, MCPA in aqueous solution (pH 9.8) produced three minor (less than 10%) photolysis products: 4-chloro-2-methyl-phenol, 4-chloro-2-formylphenol and *o*-cresol in 71 hours (Soderquist and Crosby, 1974, 1975).

- MCPA is degraded more rapidly (1 day) in soils containing less than 10% organic matter than in soil containing higher levels (3 to 9 days) (Torstensson, 1975). This may be due to adsorption to the soil organic matter. MCPA, when applied a second time to soil, is degraded twice as fast (6 to 12 days) as it is after one application (15 to 28 days). Persistence does not depend greatly upon the soil type (Loos et al., 1979).

- Unlabeled MCPA in rice paddy water under dark conditions is totally degraded by aquatic microorganisms in 13 days (Soderquist and Crosby, 1974, 1975).

- MCPA would be expected to leach readily in most soils. Phytotoxic levels of MCPA leached 30 cm in a sandy soil column eluted with 50 cm of water (Herzel and Schmidt, 1979). Using soil thin-layer chromatographic techniques, MCPA was mobile (R_f 0.6 to 1.0) in calcium montmorillonite clay (Helling, 1971) and in sandy loam, silt loam, and silty clay loam soils (Helling and Turner, 1968). Mobility increases as organic matter content decreases, possibly due to adsorption of MCPA to this soil component.

- MCPA does not volatilize from aqueous solution (pH 7.0) heated for 13 days at 34 to 35°C (Soderquist and Crosby, 1974, 1975).

- In the aquatic environment, MCPA disipates rapidly (14 to 32 days) in water, but residue levels in the flooded soil remain unchanged (Soderquist and Crosby, 1974, 1975; Sokolov et al., 1974, 1975). A common metabolite, 5-chloro-*o*-cresol, is formed at low levels (1.3% or less) within 1 day of treatment.

- In the forest ecosystem, MCPA remains in soil (0 to 3 cm) and leaf litter at 0.7 and 32 ppm, respectively, 10 months after application at 2.5 kg active ingredient per hectare (ai/ha) (Eronen et al., 1979). MCPA residues in moss decline to 7% of the initial level within 40 days. Residues in soil (3 to 15 cm deep) are not detectable after 40 days.

III. PHARMACOKINETICS

Absorption

- ° No information on the absorption of MCPA was found in the available literature.

Distribution

- ° Elo and Ylitalo (1979) treated rats with 8 mg of ^{14}C-MCPA [98% active ingredient (a.i.)] intravenously and measured the distribution of radioactivity in nine tissues 1.5 hours after treatment. Highest levels were found in plasma, kidney, lung, liver and heart with lesser amounts found in brain/cerebrospinal fluid (CSF), testis and muscle. Prior treatment of rats with MCPA (intravenous injections of 25 to 500 mg/kg 3 hours before administration of radiolabeled compound or chronic exposure to 500 or 2,500 mg/L in drinking water) lead to decreased levels of ^{14}C-MCPA in the plasma and kidney and increased levels in brain/CSF.

- ° Elo and Ylitalo (1977) treated rats with 8 mg of ^{14}C-MCPA (purity not specified) intravenously and measured the distribution of radioactivity in brain, CSF, muscle, liver and kidney 1.5 to 120 hours after treatment. Prior treatment of rats with MCPA (subcutaneous injections of 250 or 500 mg/kg) caused a decrease in the amount of radioactivity found in the plasma. Increased levels were found in other tissues with the largest increases found in the CSF (39- to 67-fold) and brain (11- to 16-fold).

Metabolism

- ° MCPA is metabolized by the liver. Stimulation of microsomal oxidation by phenobarbital increases the rate of MCPA breakdown (Buslovich et al., 1979). Gaunt and Evans (1961) found that 5-chloro-methyl-catechol is one of the metabolites of MCPA (Hattula et al., 1979).

Excretion

- ° In studies by Fjeldstad and Wannag (1977), four healthy human volunteers each ingested a dose of 5 mg of MCPA (purity not specified). Approximately 50% (2.5 mg) of the dose was detected in the urine within several days. Urinary levels were not detectable on the fifth day following exposure.

- ° Rats treated orally with MCPA (purity not specified) excreted nearly all of the MCPA during the first 24 hours after intake (90% in urine and 7% in feces) (Elo, 1976).

IV. HEALTH EFFECTS

Humans

Short-term Exposure

° Case reports of attempted suicide by ingestion of MCPA have been published (Jones et al., 1967; Johnson et al, 1965; Geldmacher et al., 1966). Symptoms included pinpoint pupils, diminished/absent reflexes, low blood pressure, spasms, unconsciousness, and death. Dose estimates were not reported.

° Palva et al. (1975) reported one case of MCPA (purity not specified) exposure (dose and duration not specified) in a farmworker involved in spraying operations. The farmer exhibited reversible aplastic anemia, muscular weakness, hemorrhagic gastritis and signs of slight liver damage that were later followed by pancytopenia of all of the myeloid cell lines. In a followup study of the exposed farmer, Timonen and Palva (1980) reported the occurrence of acute myelomonocytic leukemia.

Long-term Exposure

° No information on the human health effects of chronic exposure to MCPA was found in the available literature.

Animals

Short-term Exposure

° Gurd et al. (1965) reported an acute oral LD_{50} value for MCPA (purity not specified) of 560 mg/kg in mice. Oral LD_{50}'s for MCPA in mice of 550 mg/kg and 700 mg/kg/day in rats were reported in RTECS (1985).

° Elo et al. (1982) showed that MCPA (sodium salt; 99% a.i.) causes a selective damage of the blood-brain barrier. These authors observed that the penetration of intravenous tracer molecules such as ^{14}C-MCPA, ^{14}C-PABA, ^{14}C-sucrose, ^{14}C-antipyrine and iodinated human albumin (^{125}I-HA) in the brain and CSF of MCPA-intoxicated rats (200 to 500 mg/kg, sc) was increased compared to controls. The tissue-plasma ratios of ^{14}C-sucrose, ^{14}C-antipyrine and ^{125}I-HA treated rats were also increased in the brain and CSF of intoxicated animals, but the increases were less pronounced than those of ^{14}C-MCPA or ^{14}C-PABA.

° In oral studies by Vainio et al. (1983), Wistar rats administered the iso-octyl ester of MCPA (purity not specified) at doses of 0, 100, 150 or 200 mg/kg/day, 5 days per week for 2 weeks, showed hypolipidemia and peroxisome proliferation in the liver. A Lowest-Observed-Adverse-Effect Level (LOAEL) of 100 mg/kg was identified.

Dermal/Ocular Effects

° Raltech (1979) reported acute dermal LD_{50} values for MCPA (purity not specified) in rabbits of 4.8 g/kg for males and 3.4 g/kg for females.

- In acute dermal studies conducted by Verschuuren et al. (1975), an aqueous paste of MCPA (80.6% a.i.) (0.5 g) was applied to the abraded skin of five chinchilla rabbits. Slight erythema resulted; the skin became sclerotic after 5 to 6 days and healed by 12 days.

- In subacute dermal studies, Verschuuren et al. (1975) applied an aqueous paste of MCPA (80.6% active ingredient; 0, 0.5, 1.0 or 2.0 g) five times weekly for 3 weeks to the shaved skin of rabbits. Slight to moderate erythema occurred at all dose levels, and elasticity of the skin was decreased. The effects subsided at 2 weeks post-treatment. Weight loss was observed at all dose levels. High mortality and histopathological alterations were observed in the liver, kidneys, spleen and thymus at the 1.0- and 2.0-g dose levels.

Long-term Exposure

- Verschuuren et al. (1975) administered MCPA (80.6% a.i.) in the diet for 90 days to SPF weanling rats (10/sex/dose) at levels of 0, 50, 400 or 3,200 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0, 2.5, 20 or 160 mg/kg/day. Following treatment, growth, food intake, mortality, hematology, blood and liver chemistry, organ weights and histopathology were measured. No compound-related effects were reported for any of these parameters except for growth retardation and elevated relative kidney weights at 400 ppm (20 mg/kg/day) or more. A No-Observed-Adverse-Effect Level (NOAEL) of 50 ppm (2.5 mg/kg/day) and a LOAEL of 400 ppm (20 mg/kg/day) were identified.

- Holsing and Kundzin (1970) administered MCPA technical (considered to be 100% a.i.) in the diet of Charles-River CD rats (10/sex/dose) for 3 months. Doses were reported as 0, 4, 8 or 16 mg/kg/day; the concentration in the diet was not specified. Following treatment, no compound-related effects were observed in the physical appearance, behavior, growth, food consumption, survival, clinical chemistry, organ weights, organ-tobody weight ratios, gross pathology or histopathology at any dose tested, except for increases in kidney weight in males at 16 mg/kg/day. A NOAEL of 8 mg/kg/day and a LOAEL of 16 mg/kg/day were identified by this study.

- Holsing and Kundzin (1968) administered oral doses of MCPA technical to Charles-River CD rats at dose levels of 0, 25, 50, and 100 mg/kg/day for 13 weeks. Cytopathological changes in the liver and kidneys were observed at all doses. Kidney effects included focal hyperplasia of the epithelial lining, interstitial nephritis, tubular dilation and/or hypertrophy. A LOAEL of 25 mg/kg/day (the lowest dose tested) is identified by this study.

- Reuzel and Hendriksen (1980) administered MCPA (94% a.i.) in feed to beagle dogs in two separate 13-week studies. Dosing regimens of 0, 3, 12 or 48 mg/kg/day, and 0, 0.3, 1 or 12 mg/kg/day, respectively, were employed. Decreased kidney and liver function, characterized by increases in blood urea, SGPT and creatinine were observed at doses as low as 3 mg/kg/day. Low prostatic weight and mucopurulent conjunctivitis were observed at higher doses. A NOAEL of 1 mg/kg/day and a LOAEL of 3 mg/kg/day were identified by these studies.

- Hellwig (1986) administered oral doses of MCPA (95% a.i.) to dogs at doses of 0, 6, 30, or 150 ppm for 1 year. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg (Lehman, 1959), these levels correspond to doses of 0, 0.15, 0.75 or 3.75 mg/kg/day. Renal toxicity was observed at the two highest doses and was characterized by elevated serum levels of creatinine, urea and potassium, coloration of the kidneys and increased storage of pigment in the renal tubules. A NOAEL of 0.15 mg/kg/day and a LOAEL of 0.75 mg/kg/day were identified by this study.

- Holsing (1968) administered oral doses of MCPA (considered to be 100% a.i.) by capsule at 0, 25, 50 or 75 mg/kg/day to beagle dogs (three/sex/dose) for 13 weeks. Histopathological changes and alterations in various hematologic and biochemical parameters indicative of bone marrow, liver and kidney damage were observed at all dose levels. The hematological findings included decreased hematocrit, hemoglobin and erythrocyte counts. Several dogs had elevated blood urea nitrogen, serum glutamic-pyruvic transaminase, serum-oxaloacetic transaminase, alkaline phosphatase and serum bilirubin. Histopathological alterations were seen in the liver, kidney, lymph nodes, testes, prostate and bone marrow. All dogs of all three groups had various degrees of hepatic, renal and bone marrow injury. A LOAEL of 25 mg/kg/day (the lowest dose tested) was identified.

- Gurd et al. (1965) administered technical MCPA (purity not specified) in the feed to rats (five/sex/dose) for 7 months at dose levels of 0, 100, 400, 1,000 or 2,500 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 5, 20, 50 or 125 mg/kg/day. Following treatment, there was a marked decrease in body weight gain at 1,000 ppm (50 mg/kg/day) or 2,500 ppm (125 mg/kg/day), and some deaths occurred at 2,500 ppm (125 mg/kg/day). At 400 ppm (20 mg/kg/day) or greater, there was a reduction in numbers of red blood cells, hemoglobin content and hematocrit. Relative kidney weights were increased at 100 ppm (5 mg/kg/day), but no effects on body weight were evident. No histopathological changes were reported at any dose level tested. A LOAEL of 5 mg/kg/day (the lowest dose tested) was identified.

Reproductive Effects

- No effects on reproduction were found in rats exposed to doses of 0, 50, 150, or 450 ppm MCPA (95% a.i.) in the diet over a period of two generations (MacKenzie, 1986). Assuming that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 2.5, 7.5 or 22.5 mg/kg/day. Body weight depression was observed in the F_1 and F_2 generations at the two highest doses. A NOAEL of 22.5 mg/kg/day was identified for reproductive function, and a NOAEL of 2.5 mg/kg/day was identified for fetoxtoxicity (depressed weight gain).

Developmental Effects

- Irvine et al. (1980) administered MCPA (purity not specified) (0, 5, 12, 30 or 75 mg/kg/day) by gavage to rabbits (15 to 18/dose) on days 6 to 18 of gestation. No fetotoxicity or teratogenicity was observed at any dose level tested. Body weights of the does were markedly reduced in the 75 mg/kg/day dosage group. A fetal NOAEL of 75 mg/kg/day and a maternal NOAEL of 30 mg/kg/day were identified.

- Irvine (1980) administered MCPA (purity not specified) (0, 20, 50 or 125 mg/kg/day) by gavage to pregnant CD rats (16 to 38/dose) on days 6 to 15 of gestation. No maternal or fetal toxicity or teratogenic effects were observed. A NOAEL of 125 mg/kg/day (the highest dose tested) was identified.

- Palmer and Lovell (1971) administered oral doses of MCPA (75% a.i.; 0, 5, 25 or 100 mg/kg/day of the active ingredient) to mice (20/dose) on days 6 to 15 of gestation. Dams were monitored for pregnancy rate, body weight, and gross toxicity; no significant effects were observed. At 100 mg/kg/day, fetal weights were significantly reduced and there was delayed skeletal ossification. A NOAEL of 25 mg/kg/day and a LOAEL of 100 mg/kg/day based on fetal weights were identified.

Mutagenicity

- Moriya et al. (1983) reported that MCPA (purity not specified) (5,000 ug/plate) did not produce mutagenic activity in Salmonella typhimurium (TA 100, TA 98, TA 1535, TA 1537, TA 1538) or in Escherichia coli (WP2 hcr) either with or without metabolic activation.

- In studies conducted by Magnusson et al. (1977), there were no effects on chromosome disjunction, loss or exchange in Drosophila fed MCPA at 250 or 500 ppm.

- In studies by Linnainmaa (1984), no increases were observed in the frequency of sister chromatid exchange (SCE) in blood lymphocytes from rats intragastrically administered MCPA (purity not specified) at 100 mg/kg/day for 2 weeks. A slight increase in SCE was observed in bone marrow cells from Chinese hamsters given daily oral doses of 100 mg/kg for 2 weeks. In Chinese hamster ovarian cell cultures, SCE was slightly increased following treatment with MCPA (10^{-5}, 10^{-4}, 10^{-3}M, 1 hour) with and without activation.

Carcinogenicity

- No information on the potential carcinogenicity of MCPA was found in the available literature. However, MCPA stimulates liver peroxisomal proliferation, which has been implicated in carcinogenicity (Vainio et al., 1983).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\underline{\quad}\ \text{L/day})} = \underline{\quad}\ \text{mg/L}\ (\underline{\quad}\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for MCPA. It is therefore recommended that the Longer-term HA value for a 10-kg child (0.1 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

Several reproductive/developmental toxicity studies have been performed in which rats or rabbits have been given oral doses of MCPA for acute duration (Irvine, 1980; Irvine et al., 1980; Palmer and Lovell, 1971; MacKenzie, 1986). The only signs of maternal toxicity observed in these studies was a reduction in body weight in rats exposed to 75 mg/kg (Irvine, 1980). Estimates of maternal NOAELs range from 30 to 125 mg/kg/day (Irvine, 1980; Irvine et al, 1980). In contrast, fetotoxicity has been observed at dose levels as low as 7.5 mg/kg/day (MacKenzie, 1986). These studies were judged to be inadequate for evaluating the toxicity of MCPA from acute oral exposure, especially with respect to kidney toxicity observed after longer durations of exposure. It is therefore recommended that the Longer-term HA value for a 10-kg child of (0.1 mg/L, calculated below) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

Evidence of renal dysfunction has been observed in both 13-week (Reuzel and Hendriksen, 1980; Holsing, 1968) and 1-year (Hellwig, 1986) feeding studies in beagle dogs and serves as the basis for the Longer-term HA. In subchronic studies, changes in blood urea and creatinine levels have been observed at doses of

25 mg/kg/day (Holsing, 1968) and 3 mg/kg/day (Reuzel and Hendriksen, 1986). Renal toxicity is not unique to dogs and has been observed in rats after 90-day exposure at dose levels of 20 mg/kg/day (Verschuuren et al., 1975) and 25 mg/kg/day (Holsing, 1968). The rat and dog may have similar sensitivities; a conservative estimate of the NOAEL was obtained from the studies described by Reuzel and Hendriksen (1980). In these studies, oral doses of 0, 3, 12 or 48 mg/kg/day, and 0, 0.3, 1 or 12 mg/kg/day, respectively, were administered to dogs for 13 weeks. Increases in blood urea, SGPT and creatinine levels were observed at dose levels as low as 3 mg/kg/day; low prostatic weight and mucopurulent conjunctivitis were observed at higher dose levels. A NOAEL of 1 mg/kg/day was identified by these studies.

Using a NOAEL of 1 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.0\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.1\ \text{mg/L}\ (100\ \text{ug/L})$$

where:

1.0 mg/kg/day = NOAEL, based on the absence of renal effects in dogs exposed to MCPA in the diet for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA of NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.0\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 0.4\ \text{mg/L}\ (400\ \text{ug/L})$$

where:

1.0 mg/kg/day = NOAEL, based on the absence of renal effects in dogs exposed to MCPA in the diet for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The chronic toxicity study in dogs (Hellwig, 1986) has been selected to serve as the basis for the determination of the Lifetime HA. Beagle dogs were exposed to 0, 6, 30 and 150 ppm (0.15, 0.75, or 3.75 mg/kg/day) for 1 year. Renal toxicity was observed at the two highest doses and was characterized by elevated serum levels of creatinine, urea and potassium, coloration of the kidneys and increased storage of pigment in the renal tubules. A NOAEL of 0.15 mg/kg/day was identified, which is supported by the findings from subchronic feeding studies. From 90-day feeding studies, NOAELs of 1 mg/kg/day and 2.5 mg/kg/day have been identified for dogs (Reuzel and Hendriksen, 1980) and rats (Verschuuren et al., 1975), based on the absence of effects on the kidney seen at higher doses. In a 7-month feeding study, Gurd (1965) observed increased kidney weight in rats exposed to doses as low as 5.0 mg/kg/day, the lowest dose tested.

Using a NOAEL of 0.15 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.15\ \text{mg/kg/day})}{(100)\ (3)} = 0.0005\ \text{mg/kg/day}$$

where:

0.15 mg/kg/day = NOAEL, based on the absence of kidney effects in dogs exposed to MCPA in the diet for 1 year.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = additional uncertainty factor, used to account for the incomplete database on chronic toxicity.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.0005 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.02 \text{ mg/L } (20 \text{ ug/L})$$

where:

0.0005 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.02 mg/L) (20%) = 0.004 mg/L (4 ug/L)

where:

0.02 = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No studies on the carcinogenic potential of MCPA were found in the available literature.
- The International Agency for Research on Cancer (IARC, 1983) classified the potential carcinogenicity of MCPA in both humans and laboratory animals as indeterminate.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), MCPA may be classified in Group D: not classified. This category is used for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The National Academy of Sciences has recommended an ADI of 0.00125 mg/kg/day and a Suggested-No-Adverse-Response-Level (SNARL) of 0.009 mg/L, based on a LOAEL of 1.25 mg/kg/day in a 90-day study in rats (NAS, 1977).
- Residue tolerances have been established for MCPA at 0.1 ppm in milk and meat. Feed and forage residue tolerances range from 0.1 to 300 ppm (U.S. EPA, 1985a).

VII. ANALYTICAL METHODS

- Analysis of MCPA is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated acid pesticides in water samples (U.S. EPA, 1985b). In this method, approximately 1 liter of sample is acidified. The compounds are extracted with ethyl ether using a separatory funnel. The derivatives are hydrolized with potassium hydroxide, and extraneous organic material is removed by a solvent wash. After acidification, the acids are extracted and converted to their methyl esters using diazomethane as the derivatizing agent. Excess reagent is removed, and the esters are determined by electron-capture GC. The method detection limit has been estimated at 249 ug/L for MCPA.

VIII. TREATMENT TECHNOLOGIES

- Oxidation by ozone of 500 mg/L MCPA, after 50 to 80% disappearance of initial compound, produced no identifiable degradation products (Legube et al., 1981). This indicates that oxidation by ozone may be a possible MCPA removal technique.

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*Confidential Business Information submitted to the Office of Pesticide

August, 1988

METHOMYL

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

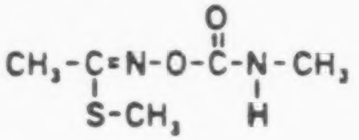
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 16752-77-5

Structural Formula



$$\mathrm{CH_3-\underset{\displaystyle S-CH_3}{\underset{|}{C}}=N-O-\overset{\displaystyle O}{\overset{\|}{C}}-\underset{\displaystyle H}{\underset{|}{N}}-CH_3}$$

S-Methyl-N[(methylcarbamoyl)oxy]-thioacetimidate

Synonyms

- ° Dupont Insecticide 1179; Dupont 1179; Insecticide 1,179; Insecticide 1179; IN 1179, Lannate; Mesomile; Nudrin; SD 14999; WL 18236 (Meister, 1983).

Uses

- ° Methomyl is a carbamate insecticide used to control a broad spectrum of insects in agricultural and ornamental crops (Meister, 1983).

Properties (Meister, 1983; Windholz et al., 1983; Cohen, 1984; CHEMLAB, 1985; and TDB, 1985)

Chemical Formula	$C_5H_{10}O_2N_2S$
Molecular Weight	162.20
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	78 to 79°C
Density (24°C)	1.29
Vapor Pressure (25°C)	5×10^{-5} mm Hg
Specific Gravity	1.29
Water Solubility (25°C)	10,000 mg/L
Log Octanol/Water Partition Coefficient	-3.56
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- ° Methomyl has been found in 1 of 423 surface water samples analyzed at a concentration of 2 ug/L, and was not found in 1,374 ground water samples analyzed (STORET, 1988). Samples were collected at 145 surface water locations and 1,326 ground water locations. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- In laboratory and greenhouse studies, methomyl was more rapidly degraded in a sandy loam and a California soil than in silt loam soils, with 21, 31, and 44 to 48% of the applied methomyl remaining in the respective soils 42-45 days after treatment. The major degradation product was carbon dioxide, which accounted for 23 to 47% of the applied methomyl after 42 to 45 days. A minor degradation product, S-methyl-N-hydroxy-thioacetimidate (a possible hydrolysis product), was also found. Methomyl half-lives were less than 30 days in sandy loam soil, less than 42 days in California soil, and approximately 45 days in muck and silt loam soils. In a sterilized Flanagan silt loam soil, 89% of the methomyl remained 45 days after application, indicating that methomyl degradation in soil is primarily a microbial process (Harvey, 1977a,b).

- The nitrogen-fixing ability of some bacteria was severely reduced (by as much as 85%) when methomyl was applied at 20 to 160 ppm (Huang, 1978).

- In another study, methomyl (18 ppm) had no effect on fungal and bacterial population or on carbon dioxide production in either silt loam or fine sand soils (Peeples, 1977).

- No methomyl residues were detected in a muck soil 7 to 32 days after treatment (E.I. DuPont de Nemours and Co., 1971).

III. PHARMACOKINETICS

Absorption

- Single oral doses of 1-^{14}C-methomyl (purity not specified) were administered via gavage to female CD rats as a suspension in 1% aqueous methylcellulose. Ninety-five percent of the dose could be accounted for in excretory products or tissue residues, indicating virtually complete absorption from the gastrointestinal tract (Andrawes et al, 1976).

- Baron (1971) reported that in rats given a single oral dose of 5 mg/kg of 1-^{14}C-labeled methomyl (purity not specified), approximately 2% of the original label was excreted in the feces after 3 days, indicating essentially complete gastrointestinal absorption.

Distribution

- Baron (1971) fed a single oral dose of 1-^{14}C-labeled methomyl (5 mg/kg, purity not specified) to rats and analyzed 13 major tissues for residues at 1 and 3 days after dosing. Only 10% of the label was present in tissues 24 hours after dosing, with no evidence of accumulation at any site. By this time, over 40% of the label had been excreted via the lung. At 3 days after dosing, tissue residues were essentially unchanged from day 1, suggesting incorporation of label into tissue components.

- Baron (1971) reported that feeding methomyl to a lactating cow at levels of 0.2 or 20 ppm in the diet (duration not specified) resulted in very low residues (less than 0.02 ppm) in the milk, meat, fat, liver and kidney.

Metabolism

- According to Baron (1971), in 72 hours approximately 15 to 23% of a 5-mg/kg oral dose of 1-^{14}C-labeled methomyl in rats could be accounted for as carbon dioxide, 33% as another metabolite in expired air, and 25% as metabolites in the urine.

- Harvey (1974) reported that in the rat, 1-^{14}C-labeled methomyl (dose and purity not specified) was metabolized to carbon dioxide (25%) or acetonitrile (50%) within 72 hours.

- Andrawes et al. (1976) reported that single oral doses of 4 mg/kg were rapidly metabolized in the rat. In exhaled air, carbon dioxide and acetonitrile were the major metabolites. In 24-hour urine samples, polar metabolites (80%) and acetonitrile (18%), both free and conjugated, were found with free methomyl, the oxime and the sulfoxide oxime detected at low levels.

- Dorough (1977), in a series of studies with ^{14}C-labeled isomeric forms of methomyl, confirmed the report by Harvey (1974) of the excretion of labeled carbon dioxide and acetonitrile in the expired air of treated rats. In addition, nearly complete (79 to 84%) hydrolysis of the ester linkage was apparent within 6 hours, prior to the major formation of carbon dioxide and acetonitrile from methomyl. The author suggested the following pathway: partial isomerization of methomyl is followed by hydrolysis of the two isomeric forms to yield two isomeric oximes that then break down to carbon dioxide and acetonitrile at different rates. No additional metabolites were identified.

Excretion

- Baron (1971) stated that within 72 hours after receiving a single oral dose of 1-^{14}C-labeled methomyl, rats excreted 15 to 23% as carbon dioxide, 33% as other metabolites in the expired air and approximately 16 to 27% as methomyl and metabolites in the urine.

- Harvey (1974) reported that 75% of an oral dose of 1-^{14}C-labeled methomyl (dose and purity not specified) was excreted by rats within 72 hours, 50% as acetonitrile and 25% as carbon dioxide in the expired air. In contrast to other carbamates, sulfur-containing metabolites were not found in the urine.

- Andrawes et al. (1976) reported that single oral doses (4 mg/kg) of 1-^{14}C-labeled methomyl were rapidly excreted, with 32% of the dose recovered in urine, 19% in feces and 40% in exhaled air after 4 days.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- Liddle et al. (1979) reported a case of methomyl poisoning in Jamaica, W.I., involving five men who had eaten a meal that included unleavened bread. Methomyl was discovered in an unlabeled plastic bag in a tin can, and had evidently been used as salt in preparation of the bread. Approximately 3 hours after the meal, the men were found critically ill, frothing at the mouth, twitching and trembling. Three were dead on arrival at the hospital. One of the two survivors showed generalized twitching and spasms, fasciculation, and respiratory impairment thought to be due to severe bronchiospasms. The other patient walked unaided and appeared generally normal. Both patients were given atropine intravenously, and the symptomatic patient recovered within 2 hours after treatment. Methomyl was confirmed in the stomach contents of each of the men who died, and analysis of the bread indicated that it contained 1.1% methomyl. It was stated that two of the victims had eaten about 75 to 100 g of bread each, or 0.82 to 1.1 g of methomyl. From these data it may be calculated that a dose of 12 to 15 mg/kg body weight can be fatal in humans.

- Araki et al. (1982) reported a case of a 31-year old woman who committed suicide, giving methomyl in drinks to herself and her two children. The 9-year-old elder son survived. In autopsies performed on the mother and the 6-year-old son, the mucous membranes of the stomach were blackish-brown, markedly edematous and congested. The lungs were heavy and congested. On the basis of measured stomach contents and tissue levels, it was estimated that the total doses taken were 2.75 g (55 mg/kg) by the mother and 0.26 g (13 mg/kg) by the child.

Long-term Exposure

- Morse and Baker (1979) reported on a survey of the health of workers in a plant that manufactured methomyl. The plant had also manufactured propanil, an herbicide manufactured from 3,4-dichloroaniline. The plant employed 111 workers in seven job categories. A complete work history, symptoms or history of poisoning, personal habits, and sources of other chemical exposure were obtained. Blood samples were collected from 100 of the 111 workers (96% males). Blood chemistries, blood counts, and cholinesterase (ChE) determinations were carried out. A routine urinalysis was also performed. Average employment at the plant was 2 years. Packaging workers had the highest rate of adverse symptoms: small pupils (46%), nausea and vomiting (46%), blurred vision (46%) and increased salivation (27%). Biomedical examination did not demonstrate significant effects, and acetylcholinesterase findings were normal. Other effects, such as chloracne, were reported but were considered related to propanil exposure.

Animals

Short-term Exposure

- The acute oral LD_{50} reported for methomyl in the fasted male and female rat ranges from 17 to 24 mg/kg (Bedo and Cieleszky, 1980; Dashiell and Kennedy, 1984; Kaplan and Sherman, 1977). The oral LD_{50} in the nonfasted rat was [illegible] mg/kg (Dashiell and Kennedy, 1984). Clinical signs in rats included [illegible] salivation, lacrimation, bulging eyes, fasciculations and tremors characteristic of ChE inhibition.

- The acute oral LD_{50} for methomyl in the mouse ranged from 27 to 35 mg/kg (Boulton et al., 1971; El-Sebae et al., 1979).

- The oral LD_{50} in hens was 28 mg/kg and in Japanese quail, 34 mg/kg (Kaplan and Sherman, 1977).

- The 4-hour inhalation LC_{50} of methomyl in rats was 300 mg/m^3. Animals showed the typical signs of ChE inhibition, including salivation, lacrimation and tremors (ACGIH, 1984).

- Bedo and Cieleszky (1980) administered single oral doses of methomyl (purity not specified) by gavage to stock colony rats at dose levels of 0, 2, 3 or 10 mg/kg. The high dose (10 mg/kg) produced tremors in rats, and brain ChE levels were decreased. In the liver, mixed-function oxidase and glucose-6-phosphatase activity, and levels of glycogen and vitamin A were unaffected. Apparently, dose levels of 2 or 3 mg/kg did not produce these effects, but did result in increased activities of chymotrypsin, lipase, and amylase in pancreatic juice.

- Woodside et al. (1978) fed methomyl (purity not specified) in the diet to male and female Wistar rats for 7 days at dose levels of 0, 5.0, 17 or 41 mg/kg/day in males and 0, 6.3, 15 or 39 mg/kg/day in females. Body weight gain was depressed at doses of 17 and 41 mg/kg/day in the males and at 15 and 39 mg/kg/day in the females. Liver and kidney weight were also depressed at 41 mg/kg/day in the male rat and at 15 and 39 mg/kg/day in the female rat. No effects were noted at the lowest doses. This study did not mention clinical signs of toxicity, and no measurements of plasma or brain ChE activity were reported. The No-Observed-Adverse-Effect Level (NOAEL) identified in this study is 5.0 mg/kg/day.

- Bedo and Cieleszky (1980) fed methomyl (purity not specified) in the diet at levels of 0, 100, 400 or 800 ppm to young adult male and female stock colony rats for 10 days. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to 0, 5, 20 or 40 mg/kg/day. Brain ChE inhibition could not be detected at any dietary level. The only findings were increased mixed-function oxidase activity in the livers of female rats at 400 and 800 ppm. This study identified a NOAEL of 800 ppm (40 mg/kg/day).

- Kaplan and Sherman (1977) administered methomyl (90% pure) to six male Charles River CD rats at 0 or 5.1 mg/kg/day, five times a week for 2 weeks. Following treatment, survival, clinical signs, ChE activity and histopathology were evaluated. All rats survived the dosing period. Clinical signs in treated rats included chewing motions, profuse salivation, lacrimation, bulging eyes, fasciculations and tremors characteristic of ChE inhibition. The authors reported that the signs became less pronounced after the first week of dosing, indicating some degree of adaptation. Plasma ChE was comparable to control levels, and no compound-related histopathological effects were reported. A lowest-observed-adverse-effect level (LOAEL) of 5.1 mg/kg/day was identified from this study.

Dermal/Ocular Effects

- Kaplan and Sherman (1977) applied a 52.8% aqueous suspension of methomyl to the clipped, intact skin of six adult male albino rabbits and covered the area with an occlusive patch for a 24-hour period. The lethal dose was found to be greater than 5,000 mg/kg, the maximum tolerated dose.

- McAlack (1973) reported a 10-day subacute exposure of rabbit skin to methomyl. Male albino rabbits, six per dosage group, were treated with 0, 50 or 100 mg/kg/day for 10 days. The compound was diluted in water (29% solution), placed on the skin and covered with an occlusive covering for 6 hours per day. No signs of ChE inhibition were noted in any of the animals.

- Rabbits (5/sex) survived 15 daily doses of 200 mg/kg/day of methomyl applied to intact skin. When the same dose of methomyl was applied to abraded skin, rabbits showed labored respiration, nasal discharge, salivation, excessive mastication, tremors, poor coordination, hypersensitivity and abdominal hypertonia. These effects occurred within 1 hour after dosing in most animals. One animal died after the first dose, and another died after the eighth application. These deaths appeared to be compound-related (Kaplan and Sherman, 1977).

Long-term Exposure

- Kaplan and Sherman (1977) reported a 90-day feeding study in Charles River-CD rats (10/sex/group) given food containing methomyl (90% purity) at dietary levels of 0, 10, 50, 125 or 250 ppm active ingredient (a.i.). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0, 0.5, 2.5, 6.2 or 12.5 mg/kg/day. After 6 weeks, the 125-ppm dose was increased to 500 ppm (25 mg/kg/day) for the remainder of the study. Clinical signs, biochemical analyses (including plasma ChE) and urinalyses were not abnormal. In a few cases, lower hemoglobin values were observed at one month in females receiving 50 ppm (2.5 ug/kg/day) and at two months in males receiving 250 ppm. At three months, the red cell count of female rats at 250 ppm was somewhat lower than controls, but still within normal limits. These findings were consistent with moderate increases of erythroid components observed histologically in the bone marrow. Microscopic examination of all other tissues showed no consistent abnormalities. Based on these observations, this study identified a NOAEL of 50 ppm (2.5 mg/kg/day) and a LOAEL of 250 ppm (12.5 mg/kg/day).

In a 90-day study using dogs, Kaplan and Sherman (1977) fed methomyl (90% pure) to four males and four females, 11 to 13 months of age, at dietary levels of 0, 50, 100 or 400 ppm a.i. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0, 1.25, 2.5 or 10 mg/kg/day. Hematological, biochemical and urine analyses were conducted at least three times on each dog prior to the study and then at 1, 2 and 3 months during the exposure period. Body weight was monitored weekly. At necropsy, organ weights were recorded, and over 30 tissues were prepared for histopathologic examination. No effects attributable to methomyl were found during or at the conclusion of the study. Based on these data, a NOAEL of 10 mg/kg/day was identified.

Homan et al. (1978) reported a 13-week dietary study of methomyl (purity not specified) in F-344 rats. Dose levels were reported to be 0, 1, 3, 10.2, or 30.2 mg/kg/day for male rats, and 0, 1, 3, 9.9 or 29.8 mg/kg/day for female rats. There were no deaths or clinical signs of toxicity. The body weight gain of females (but not males) was significantly depressed at all dose levels from day 28 until completion of the study. Kidney weight to body weight ratios were significantly increased in female rats at the two highest dose levels, but absolute kidney weights were not significantly increased. Red blood cell ChE activity was elevated at the high dose levels, but plasma and brain ChE levels were normal at all dose levels. Histopathological examination of 31 tissues from representative high-dose and control animals revealed no significant effects. Weights of brain, liver, kidney, spleen, heart, adrenals and testes were not altered. This study identified a NOAEL of 3 mg/kg/day and a LOAEL of 9.9 mg/kg/day.

Bedo and Cieleszky (1980) reported a 90-day feeding study of methomyl in male and female rats receiving dietary levels of 100 or 200 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 5 or 10 mg/kg/day. At 200 ppm, the female rats showed decreased brain ChE activity, decreased liver vitamin A content and elevated total serum lipids. This study identified a NOAEL of 100 ppm (5 mg/kg/day).

Kaplan and Sherman (1977) reported a 22-month dietary feeding study in which Charles River-CD male and female rats were fed methomyl (90 or 100% pure) at dietary levels of 0, 50, 100, 200 or 400 ppm a.i. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0, 2.5, 5, 10 or 20 mg/kg/day. Mortality data were not reported. At autopsy, 9 of 13 males and 21 of 23 females at the 400-ppm level had kidney tubular hypertrophy and vacuolization of epithelial cells of the proximal convoluted tubules. Compound-related histological alterations were also seen in the spleens of female rats at the 200-ppm dose level. No effects were seen on ChE levels in plasma or red blood cells. This study identified a LOAEL of 200 ppm (10 mg/kg/day) and a NOAEL of 100 ppm (5 mg/kg/day).

- Kaplan and Sherman (1977) performed a 2-year feeding study in beagle dogs (four/sex/dose). Methomyl (90 or 100% pure) was supplied at dietary levels of 0, 50, 100, 400 or 1,000 ppm a.i. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 1.25, 2.5, 10 or 25 mg/kg/day. Hematological, biochemical (including plasma- and red-blood-cell ChE activity) and urine analyses were conducted once on each dog prior to the start of the study, at 3, 6, 12, 18 months during the exposure period and at 24-month sacrifice. At 1 year, one male and one female per dose group were sacrificed for histopathological examination. One female dog at the 1,000-ppm dose level died after 8 weeks in the study, and a replacement dog died after 18 days. Death was preceded by convulsive seizures and coma. These deaths appear to be compound-related. Two male dogs in the 1,000-ppm dose group showed clinical signs during week 13, including tremors, salivation, incoordination and circling movements. Hematological studies revealed slight-to-moderate anemia in five dogs (1,000-ppm dose group) at 3 months, which persisted in one dog to sacrifice. No compound-related signs or effects were noted with respect to appetite, body weight changes, biochemical studies (including ChE) and urinanalyses. Dose-related histopathological changes were seen in kidney and spleen of animals receiving 400 and 1,000 ppm. Changes were also seen in livers and bone marrow of animals receiving 1,000 ppm. Pigment deposition was noted in the epithelial cells of the proximal convoluted tubules of the kidney in males at 400 and 1,000 ppm and in females at 1,000 ppm. A minimal-to-slight increase in bile duct proliferation and a slight increase in bone marrow activity was seen in animals receiving 1,000 ppm. The authors concluded that histological results indicated a NOAEL of 100 ppm (2.5 mg/kg/day). Minimal histopathological changes seen in the kidneys and spleen of animals receiving 400 ppm (10 mg/kg/day), identified this level as the LOAEL.

- Hazelton Laboratories (1981) reported a 2-year study of methomyl (99% purity) in mice. Male and female CD-1 mice (80/sex/dose) were fed methomyl in the diet at dose levels of 0, 50, 100, or 800 ppm for 104 weeks. Assuming 1 ppm in the diet to be equivalent to 0.15 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0, 7.5, 15 or 120 mg/kg/day. Survival was significantly reduced (no details provided) in both males and females at the 800-ppm dose level by week 26. The 800 ppm dose level was reduced to 400 ppm (1.0 mg/kg/day) at week 28 and then further reduced to 200 ppm (30 mg/kg/day) at week 39. At week 39, the 100 ppm was decreased to 75 ppm (11.2 mg/kg/day). Survival was depressed in all groups of treated males at 104 weeks. No compound-related histopathological changes were noted in tissues of animals necropsied at 104 weeks. A LOAEL of 50 ppm (7.5 mg/kg/day; the lowest dose tested) may be identified based on decreased survival.

- Haskell Laboratories (1981) reported a 2-year study of methomyl (99% purity) in rats. Charles River C-D rats (100/sex/dose) were fed methomyl in the diet at dose levels of 0, 50, 100 or 400 ppm for up to 2 years. Assuming 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 2.5, 5 or 20 mg/kg/day. Effects seen in the 400 ppm group include reduced weight gain in both sexes, and in females, lower erythrocyte counts, hemoglobin values and hematocrits. Blood and brain cholinesterase levels were within the range as were other clinical chemistry parameters. A NOAEL of 5 mg/kg/day and a LOAEL of 20 mg/kg/day were idnetified from this study.

Reproductive Effects

- Male and female weanling Charles River-CD rats were fed methomyl (90% pure) at dietary levels of 0, 50, or 100 ppm a.i. for 3 months. Assuming that 1 ppm in the diet of weanling rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to about 0, 2.5 or 5 mg/kg/day. Ten males and twenty females from each group were bred and continued on the diet through three generations. No adverse effects were reported on reproduction or lactation, and no pathologic changes were found in the weanling pups of the F_{3b} generation (Kaplan and Sherman, 1977). A NOAEL of 5 mg/kg/day was identified from the highest dose tested.

Developmental Effects

- New Zealand White rabbits, five per group, were dosed with 0, 2, 6 or 16 mg/kg of methomyl (98.7% pure) on days 7 through 19 of gestation. One animal died at the 16 mg/kg dose level, exhibiting characteristic signs of ChE inhibition, including tremors, excitability, salivation and convulsions. No adverse effects were observed at any dose level on embryo viability or on the frequency of soft-tissue or skeletal malformations (Feussner et al., 1983). This study identified a maternal NOAEL of 6 mg/kg and a teratogenic NOAEL of 16 mg/kg/day, the highest dose tested.

- Kaplan and Sherman (1977) fed methomyl (90% pure) to pregnant New Zealand White rabbits on days 8 to 16 of gestation at dietary levels of 0, 50 or 100 ppm active ingredient. Assuming that 1 ppm in the diet of rabbits is equivalant to 0.03 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0, 1.5 or 3 mg/kg/day. One-third of the fetuses were stained with Alizarin Red S and examined for skeletal defects. Since no soft tissue or skeletal abnormalities were observed at any dose level tested, a NOAEL of 3 mg/kg/day was identified.

Mutagenicity

- Methomyl has been reported to be negative in the Ames test utilizing Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 without metabolic activation (Blevins et al., 1977; Moriya et al., 1983). Waters et al. (1980) reported methomyl as negative with and without metabolic activation in strains TA 100, TA 1535, TA 1537 and TA 1538.

Carcinogenicity

- Kaplan and Sherman (1977) fed ChR-CD rats (35/sex/dose) methomyl (90% pure) in the diet at levels of 0, 50, 100, 200 or 400 ppm active ingredient for 22 months. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to about 0, 2.5, 5, 10 or 20 mg/kg/day. Gross and histological examination revealed no increased tumor incidence in either male or female rats.

- Haskell Laboratories (1981) report on a study in which Charles River C-D rats (100/sex/group) were administered methomyl (99% pure) in the diet at dietary levels of 0, 50, 100 or 400 ppm for two years. Gross and histological examination revealed no increase in tumor incidence in either sex.

- Hazelton Laboratories (1981) reported the results of a 2-year study of methomyl (purity not specified) in CD-1 mice (80/sex/dose). Initial dose levels were 0, 50, 100, or 800 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these doses correspond to 0, 7.5, 15 or 120 mg/kg/day. Because of early mortality, the 800-ppm dose was reduced to 400 ppm (60 mg/kg/day) at week 28, and then to 200 ppm (30 mg/kg/day) at week 39. At week 29, the 100-ppm dose was reduced to 75 ppm (11.2 mg/kg/day). Histological examination at necropsy did not reveal any treatment-related effects on tumor incidence.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-Day Health Advisory

No information found in the available literature was suitable for determination of the One-day HA value for methomyl. It is, therefore, recommended that the Longer-term HA (0.3 mg/L), be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The health effects associated with acute and subchronic exposure to methomyl are primarily associated with cholinesterase (ChE) inhibition. Symptoms of ChE inhibition have been shown in rats administered methomyl via gavage at doses as low as 5.1 mg/kg/day for 2 weeks (Kaplan and Sherman, 1977). Methomyl incorporated into the diet may have less dramatic effects; no ChE effects were observed in rats exposed subchronically to methomyl at dietary levels of 100 ppm, equivalent to a dose of 5 mg/kg/day (Kaplan and Sherman, 1977; Bedo and Cieleszky, 1980). A similar NOAEL, 2.5 mg/kg/day, was found for lifetime studies in dogs (Kaplan and Sherman, 1977). No controlled human studies have been performed, but human fatalities from methomyl ingestion after a single exposure to an estimated dose of 12 mg/kg in bread or 13 mg/kg in drinks have been reported (Liddle et al., 1979; Araki et al., 1982).

Because the timing and nature of administration can profoundly affect the expression of methomyl toxicity, and little margin of safety can be expected between doses that are fatal and those that cause little or no acute toxicity, the available acute studies were judged to be inadequate for the basis of the Ten-day HA value. Therefore, it is recommeded that the Longer-term HA for a 10-kg child (0.3 mg/L), be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The onset of subchronic or chronic methomyl toxicity appears to occur at doses similar to those that cause acute toxicity. Acute ChE inhibition has been reported to occur at doses as low as 5.1 mg/kg/day for rats exposed via gavage, and human fatalities from ingestion of approximate methomyl doses of 12 mg/kg in bread and 13 mg/kg in drinks have been reported (Liddle et al, 1979; Araki et al., 1982). Kidney toxicity (increased kidney weight and hypertrophy) in acute, subchronic and chronic conditions has been reported at doses of 15, 9.9 and 10 mg/kg/day, respectively (Woodside et al., 1978; Homan et al., 1978; Kaplan and Sherman, 1977). Because of the severity of the toxic effects, the most conservative estimate of the NOAEL (2.5 mg/kg/day from the chronic study in dogs; Kaplan and Sherman, 1977), was selected as the basis for the Longer-term HA. In this study, beagle dogs were exposed to methomyl in the diet at approximate doses of 0, 1.25, 2.5, 10, or 25 mg/kg/day for 2 years. Dogs receiving 1.25 or 2.5 mg/kg/day showed no evidence of toxic effects while those receiving the two highest doses exhibited histopathological changes in the kidney and spleen. Based on a NOAEL of 2.5 mg/kg/day, the Longer-term HA for the child and adult are calculated as follows:

$$\text{Longer-term HA}_{\text{child}} = \frac{(2.5\ \text{mg/kg/day})\ (10\text{kg})}{(100)(1\ \text{L/day})} = 0.3\ \text{mg/L}\ (300\ \text{ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of effects on blood chemistry (including ChE activity), hematology, urinanalysis, histopathology or body weight in dogs exposed via the diet for 2 years.

10 kg = assumed body weight of a child

1 L/day = assumed daily water consumption of child

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

$$\text{Longer-term HA}_{\text{adult}} = \frac{(2.5\ \text{mg/kg/day})\ (70\text{kg})}{(100)(2\ \text{L/day})} = 0.9\ \text{mg/L}\ (900\ \text{ug/L})$$

where:

2.5 mg/kg/day = NOAEL based on absence of effects on blood chemistry (including ChE activity), hematology, urinanalysis, histopathology or body weight in dogs exposed via the diet for 2 years.

70 kg = assumed body weight of an adult

2 L/day = assumed daily water consumption of an adult

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Chronic exposure to methomyl in the diet induces renal toxicity in rats and dogs. Rats exposed to 900 ppm (20 mg/kg/day) for 22 months exhibited kidney tubular hypertrophy and vacuolation of the eptithelial cells, and effects on the kidney (increased weight) have also been observed in rats exposed to 9.9 mg/kg/day in the diet for 13 weeks (Homan et al., 1978). Dogs exposed to 400 ppm (10 mg/kg/day) for 2 years exhibited swelling and increased pigmentation of the epithelial cells of the proximal tubules (Kaplan and Sherman, 1977). The NOAEL of 2.5 mg/kg/day identified from the dog study is a conservative estimate of the NOAEL and serves as the basis for the Lifetime HA.

In this study, beagle dogs (4/sex/dose) were exposed to 50, 100, 400 or 1,000 ppm methomyl in the diet for 2 years (1.25, 2.5, 10 and 25 mg/kg/day). Dogs receiving 1.25 or 2.5 mg/kg/day showed no evidence of toxic effects. Those receiving 10 mg/kg/day exhibited histopathological changes in the kidney and spleen. In addition to these effects, animals receiving the highest dose also exhibited symptoms of central nervous system (CNS) toxicity, as well as liver and bone marrow effects.

Using a NOAEL of 2.5 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(2.5\ \text{mg/kg/day})}{(100)} = 0.025\ \text{mg/kg/day}$$

where:

2.5 mg/kg/day = NOAEL, based on absence of effects on blood chemistry (including ChE activity), hematology, urinalysis, histopathology or body weight in dogs exposed in the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.025\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.9\ \text{mg/L}\ (900\ \text{ug/L})$$

where:

0.025 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of adult.

Step 3: Determination of a Lifetime Health Advisory, rounded to one significant figure

Lifetime HA = (0.9 mg/L) (20%) = 0.2 mg/L (200 ug/L)

where:

0.9 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Two-year carcinogenicity studies in rats and mice (Kaplan and Sherman, 1977; Haskell Laboratories, 1981; Hazelton Laboratories, 1981) have not revealed any evidence of carcinogenicity.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of methomyl.

- Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), methomyl may be classified in Group E: no evidence of carcinogenicity. This group is used for substances that show no evidence of carcinogenicity in at least two adequate animal tests in different species or in both epidemiologic and animal studies. Two year studies in rats and mice have not revealed any evidence of carcinogenicity (Kaplan and Sherman, 1977; Haskell Laboratories, 1981; Hazelton Laboratories, 1981).

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The National Academy of Sciences (NAS, 1983) has a Suggested-No-Adverse-Response-Level (SNARL) of 0.175 mg/L, which was calculated using an uncertainty factor of 100 and a NOAEL of 2.5 mg/kg/day identified in the 2-year dog study by Kaplan and Sherman (1977).

- Residue tolerances have been established for methomyl in or on raw agricultural commodities (U.S. EPA, 1985). These tolerances are based on an ADI value of 0.025 mg/kg/day, which is based on a NOAEL of 2.5 mg/kg/day in dogs and an uncertainty factor of 100. Residues range from 0.1 (negligible) to 40 ppm.

- The World Health Organization identified a Temporary ADI of 0.01 mg/kg/day for methomyl (Vettorazzi and Van den Hurk, 1985), based on the same chronic toxicity data, but using a larger uncertainty factor than that used to derive the RfD.

- ACGIH (1984) has adopted a threshold limit value (TLV) of 0.2 mg/m^3 as a time-weighted average exposure to methomyl for an 8-hour day.

VII. ANALYTICAL METHODS

- Analysis of methomyl is by a high-performance liquid chromatographic (HPLC) procedure used for the determination of N-methyl carbamoyloximes and N-methylcarbamates in drinking water (U.S. EPA, 1988). In this method, the water sample is filtered and a 400-uL aliquot is injected into a reverse-phase HPLC column. Compounds are separated by gradient elution chromatography. After elution from the HPLC column, the compounds are hydrolyzed with sodium hydroxide. The methyl amine formed during hydrolysis is reacted with o-phthalaldehyde to form a fluorescent derivative that is detected using a fluorescence detector. This method has been validated in a single laboratory, and the estimated detection limit for methomyl is 0.5 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) adsorption will remove methomyl from water. Whittaker (1980) experimentally determined adsorption isotherms for methomyl solutions on GAC.

- Whittaker (1980) reported the results of GAC columns operating under benchscale conditions. At a flow rate of 0.8 gpm/sq ft and empty bed contact time of 6 minutes, methomyl breakthrough (when effluent concentration equals 10% of influent concentration) occurred after 124 bed volumes (BV). When a bi-solute methomyl-metribuzin solution was passed over the same column, methomyl breakthrough occurred after 55 BV.

- Treatment technologies for the removal of methomyl from water are available and have been reported to be effective (Whittaker, 1980). However, the selection of an individual technology or a combination of technologies must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

METHYL PARATHION

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

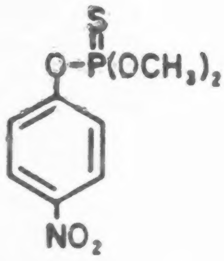
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 298-00-0

Structural Formula



O,O-Dimethyl-O-(4-nitrophenyl) phosphorothioic acid

Synonyms

- Metaphos; Dimethyl parathion; Folidol M; Metocide; Penncap M; Sinafid M-48; Wofatox; Cekumethion; Devithion; Drexel Methyl Parathion 4E; E601; Fosferno M50; Gearfos; Parataf; Partron-M; Tekwaisa; Parathion-methyl (Meister, 1988).

Uses

- A restricted-use pesticide for control of various insects of economic importance; especially effective for boll weevil control (Meister, 1988).

Properties (Hawley, 1981; Meister, 1988; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_8H_{10}O_5NSP$
Molecular Weight	263.23
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	35 to 36°C
Density	--
Vapor Pressure (20°C)	0.97×10^{-5} mm Hg
Specific Gravity	--
Water Solubility (25°C)	55 to 60 mg/L
Log Octanol/Water Partition Coefficient	3.11 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Methyl parathion has been found in 1,070 of 27,082 surface water samples analyzed and in 8 of 2,836 ground water samples (STORET, 1988). Samples were collected at 3,558 surface water locations and 2,111 ground water locations, and methyl parathion was found in 20 states. The 85th percentile of all nonzero samples was 1.18 ug/L in surface water and 0.05 ug/L in ground water sources. The maximum concentration found was 13 ug/L in surface water and 0.05 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Methyl parathion (99% pure) at 10 ppm was added to sea water and exposed to sunlight; some samples were also kept in the dark (controls). After 6 days, 57% of the parent compound had degraded but the degradates were not identified. Since only 27% of the parent compound had degraded in the dark controls, this indicates that methyl parathion is subject to photodegradation in sea water (U.S. EPA, 1981).

- The degradation rate of two formulations (EC and MCAP) of methyl parathion, applied at 0.04 ppm, was compared in a sediment/water system. Degradates were not identified; however, the parent compound had a half-life of 1 to 3 days in water. In the hydrosoil plus sediment, methyl parathion applied as an emulsifiable concentrate formulation had a half-life of 1 to 3 days, whereas for the micro-encapsulated formulation, the half-life was 3 to 7 days (Agchem, 1983).

- Methyl parathion was relatively immobile in 30-cm soil columns of sandy loam, silty clay loam and silt loam soils leached with 15.7 inches of water, with no parent compound found below 10 cm or in the column leachate, which was the case for the column of sand (Pennwalt Corporation, 1977).

- Methyl parathion (MCAP or EC formulation) at 5 lb ai/A (active ingredient/acre) was detected in runoff water from field plots irrigated 4 to 5 days posttreatment. Levels found in soil and turf plots ranged from 0.13 to 21 ppm and 0.17 to 0.20 ppm, respectively (Pennwalt Corporation, 1972).

- A field dissipation study with methyl parathion (4 lb/gal EC) at 3 lb ai/A, applied alone or in combinaton with Curacron, dissipated to nondetectable levels (<0.05 ppm) within 30 days in silt loam and loamy sand soils (Ciba-Geigy Corporation, 1978).

III. PHARMACOKINETICS

Absorption

- Braeckman et al. (1983) administered a single oral dose of ^{35}S-methyl parathion (20 mg/kg) by stomach tube to four mongrel dogs. Peak concentrations in plasma ranged from 0.13 to 0.96 ug/mL, with peak levels occurring 2 to 9 hours after dosing. In two dogs given single oral doses of ^{35}S-methyl parathion (3 mg/kg) in this study, absorption was estimated to be 77 and 79%, based on urinary excretion of label.

The authors concluded that methyl parathion was well absorbed from the gastrointestinal tract.

- Hollingworth et al. (1967) gave a single oral dose of ^{32}P-labeled methyl parathion by gavage (3 or 17 mg/kg, dissolved in olive oil) to male Swiss mice. Recovery of label in the urine reached a maximum of about 85%, most of this occurring within 18 hours of dosing. The amount of label in the feces was low, never exceeding 10% of the dose. This indicated that absorption was at least 90% complete.

Distribution

- Ackermann and Engst (1970) administered methyl parathion to pregnant albino rats and examined the dams and fetuses for the distribution of the pesticide. The pregnant rats (weighing about 270 g each) were given 3 mg (11.1 mg/kg) of methyl parathion orally on days 1 to 3 of gestation and sacrificed 30 minutes after the last dose. Methyl parathion was detected in the maternal liver (25 ng/g), placenta (80 ng/g), and in fetal brain (35 ng/g), liver (40 ng/g) and back musculature (60 ng/g).

Metabolism

- Hollingworth et al. (1967) gave ^{32}P-labeled methyl parathion by gavage (3 or 17 mg/kg, dissolved in olive oil) to male Swiss mice. About 85% of the label appeared in the urine within 72 hours. Urinary metabolites identified 24 hours after the low dose were: dimethyl phosphoric acid (53.1%); dimethyl phosphorothioic acid (14.9%); desmethyl phosphate (14.1%); desmethyl phosphorothioate (11.7%); phosphoric acid (2.0%); methyl phosphoric acid (1.7%); and phosphate (0.6%). The radioactivity in the urine was fully accounted for by hydrolysis products and P=0 activation products. No evidence was found for reduction of the nitro group to an amine, oxidation of the ring methyl group, or hydroxylation of the ring. A generally similar pattern was observed at the high dose, except for a lower percentage of dimethyl phosphoric acid (31.9%) and higher percentages of desmethyl phosphate (23.1%) and desmethylphosphorothionate (18.8%). Based on this, the authors proposed a metabolic scheme involving oxidative desulfuration, oxidative cleavage of the phospho group from the ring and hydrolysis of the phosphomethyl esters.

- Neal and DuBois (1965) investigated the in vitro detoxification of methyl parathion and other phosphorothioates using liver microsomes prepared from adult male Sprague-Dawley rats. Metabolism was found to involve oxidative desulfuration followed by hydrolysis to yield p-nitrophenol. Extracts from livers of adult male rats exhibited higher metabolic activity than that of adult females (3.2 versus 1.9 units, where one unit equals 1 ug p-nitrophenol/50 mg liver extract) ($p < 0.01$). The activity of weanling rat liver (2.7 units) was intermediate between these two. In the case of adult CF-1 mice, the activity of female liver (3.2 units) was significantly greater ($p < 0.05$) than that of the males (2.3 units). The activity of young adult male guinea pig liver extracts was 5.6 units. The authors noted that these differences in metabolic detoxification rates correlated with the sex and species differences in susceptibility to the acute oral toxic effects of this family of compounds.

- Nakatsugawa et al. (1968) investigated the degradation of methyl parathion using liver microsomes from adult male rats and rabbits (strains not specified). Metabolism occurred by two oxidative pathways: activation of the phosphorus-sulfur bond to the phosphorus-oxygen analog, and cleavage at the aryl phosphothioate bond to yield p-nitrophenol. These reactions occurred only in the presence of oxygen and $NADPH_2$. The amounts of phenol and oxygen analog formed were 3.8 and 3.7 uM in the rabbit liver extract and 2.5 and 5.4 uM in the rat liver extract, respectively.

Excretion

- Braeckman et al. (1983) administered individual doses of 3 mg/kg of ^{35}S-methyl parathion to two mongrel dogs. In each dog, the agent was given once intravenously and, 1 week later, once orally via stomach tube. This dosing pattern was repeated once in one dog. Urine was collected every 24 hours for 6 days after each treatment. Urinary excretion 6 days after oral dosing was 63% in the animal without repeated dosing and 70% and 78% in the other. Urinary excretion 6 days after intravenous dosing was 80% in the animal without repeated dosing and 95 to 96% in the other. Most of the label appeared in urine within two days. Other excretory routes were not monitored.

- Hollingworth et al. (1967) gave 32P-labeled methyl parathion (3 or 17 mg/kg, dissolved in olive oil) by gavage to male Swiss mice. Recovery of label in the urine reached a maximum of about 85%, most of this occurring within 18 hours of dosing. The amount of label in the feces was low, never exceeding 10% of the dose. This indicated that absorption was at least 90% complete.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- Nemec et al. (1968) monitored cholinesterase (ChE) levels in two workers (entomologists) who examined plants in a cotton field after it had been sprayed with an ultra-low-volume (nonaqueous) preparation of methyl parathion (1.5 to 2 lb/acre). The men entered a cotton field to examine the plants on 3 different days over a 2-week period; two of these occasions were within 2 hours after the ultra-low-volume spraying, and the third occasion was 24 hours after a spraying. After each field trip their arms were washed with acetone and the adhering methyl parathion determined. It was found that contact with the plants 2 hours after spraying resulted in 2 to 10 mg of methyl parathion residue on the arms; exposure 24 hours after spraying resulted in a residue on the arms of 0.16 to 0.35 mg. The amount of pesticide absorbed was not estimated. No toxic symptoms were experienced by either man, but measurement of red blood cell ChE activity immediately after the third of these exposures showed a decrease in activity to 60 to 65% of preexposure levels. These values did not increase significantly over the next 24 hours. It was concluded that workers should not enter such a field until more than 24 hours, and preferably 48 hours, have elapsed after spraying with ultra-low-volume insecticide sprays. Water emulsion sprays were not tested, but the authors cautioned that it cannot be assumed that they are less hazardous than the ultra-low-volume spray residues.

- Rider et al. (1969, 1970, 1971) studied the toxicity of technical methyl parathion (purity not specified) in human volunteers. Each phase of the study was done with different groups of seven male subjects, five of whom were test subjects and two were vehicle controls (Rider et al., 1969). Each study phase was divided into a 30-day pre-test period for establishing cholinesterase baselines, a 30-day test period when a specific dose of methyl parathion was given, and a post-test period.

- Thirty-two different dosages were evaluated by Rider et al. (1969), ranging from 1 to 19 mg/day. Early in the study, several of the groups were given more than one dose level during a single phase. The initial amount was 1.0 mg with an increase of 0.5 mg during each succeeding test period up to 15.0 mg/day. At this point, the dose was increased by 1.0 mg/day to a total dose of 19.0 mg/day. Pesticide in corn oil was given orally in capsules, once per day for each test period of 30 days. At no time during any of the studies were there any significant changes in blood counts, urinalyses, or prothrombin times, or was there any evidence of toxic side effects. Cholinesterase activity of the plasma and red blood cells (RBCs) was measured twice weekly prior to, during and after the dosing period. The authors considered a mean depression of 20 to 25% or greater in ChE activity below control levels to be indicative of the toxic threshold. At 11.0 mg/day, a depression of 15% in plasma ChE occurred, but doses up to and including 19 mg/day did not produce any significant ChE depression.

- Rider et al. (1970) studied the effects of 22, 24 and 26 mg/day technical methyl parathion. There were no effects observed at 22 mg/day. At 24 mg/day, plasma and RBC ChE depression was produced in two subjects, the maximum decreases being 24 and 23% for plasma, and 27 and 55% for RBC. The mean maximal decreases (in all five subjects) were 17% for plasma and 22% for RBC. With 26 mg/day RBC ChE depression was again produced in only two of the subjects, with maximum decreases of 25 and 37%. The mean maximum decrease was 18%. Plasma cholinesterase was not significantly altered.

- Rider et al. (1971) assessed the effects of 28 and 30 mg/day technical methyl parathion. At 28 mg/day, a significant decrease in RBC ChE was produced in three subjects (data not given), with a maximum mean decrease of 19%. With a dose of 30 mg/day, a mean maximum depression of 37% occurred. Based on their criteria of 20 to 25% average depression of ChE activity, the authors concluded that this was the level of minimal incipient toxicity. Body weights of the test subjects were not reported, but assuming an average body weight of 70 kg, a dose of 22 mg/day corresponds to a No-Observed-Adverse-Effect Level (NOAEL) of 0.31 mg/kg/day, and the 30 mg/day dose corresponds to 0.43 mg/kg/day. The NOAEL is considered to be 22 mg/day herein because of the apparent sensitivity of some individual subjects at higher doses to have met the 20 to 25% criteria for ChE depression as an effect.

Long-term Exposure

- No information was found in the available literature on the health effects of methyl parathion in humans.

Animals

Short-term Exposure

- Reported oral LD_{50} values for methyl parathion include 14 and 24 mg/kg in male and female Sherman rats, respectively (Gaines, 1969); 14.5 and 19.5 mg/kg in male and female CD-1 mice, respectively (Haley et al., 1975); 30 mg/kg in male ddY mice (Isshiki et al., 1983); 18.0 and 8.9 mg/kg in male and female Sprague-Dawley rats, respectively (Sabol, 1985); and 9.2 mg/kg in rats of unreported strain (Galal et al., 1977).

- Galal et al. (1977) determined the subchronic median lethal dose (C-LD_{50}) of methyl parathion (purity not specified) in adult albino rats. Groups of 10 animals received an initial daily oral dose (by gavage) of 0.37 mg/kg (4% of the acute oral LD_{50}). Every 4th day the dose was increased by a factor of 1.5 (dose based on the body weight of the animals as recorded at 4-day intervals). Treatment was continued until death or termination at 36 days. Hematological and blood chemistry analyses were performed initially and on the 21st and 36th days of the study. Histopathological studies of the liver, kidneys and heart were also carried out on the 21st and 36th days of treatment. The C-LD_{50} obtained was 13 mg/kg. The authors concluded that the most predominant hazards of subchronic exposure to methyl parathion were weight loss, hyperglycemia and macrocytic anemia, all probably secondary to hepatic toxicity. Since an increasing dose protocol was used, this study does not identify a NOAEL or a Lowest-Observed-Adverse-Effect Level (LOAEL).

- Daly et al. (1979) administered methyl parathion (technical, 93.65% active ingredient) to Charles River CD-1 mice for 4 weeks at levels of 0, 25 or 50 ppm in the diet. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to doses of about 0, 3.75 or 7.5 mg/kg/day. Five animals of each sex were used at each dose level. Mean body weights were lower ($p < 0.05$) than control for all treated animals throughout the test period. Mean food consumption was lower ($p < 0.05$) throughout for all test animals except females at the 25-ppm level. Mortality, physical observations, and gross postmortem examinations did not reveal any treatment-related effects. Cholinesterase measurements were not performed. Based on body weight gain, the LOAEL for this study was identified as 25 ppm (3.75 mg/kg/day).

- Tegeris and Underwood (1977) examined the effects of feeding methyl parathion (94.32% pure) to beagle dogs (4 to 6 months of age, weighing 5 to 10 kg) for 14 days. Two animals of each sex were given doses of 0, 2.5, 5 or 10 mg/kg/day. All animals survived the 14-day test period. Mean feed consumption and weight gain were significantly ($p < 0.05$) depressed for both sexes at the 5 and 10 mg/kg/day dose levels. After the 3rd day, animals in the high-dose group began vomiting after all meals. Vomiting was observed sporadically at the lower dose levels, particularly during the 2nd week. The authors attributed this to acetylcholinesterase inhibition, but no measurements were reported. No other symptomatology was described. Based on weight loss and vomiting, this study identified a LOAEL of 2.5 mg/kg/day in the dog.

- Fan et al. (1978) investigated the immunosuppressive effects of methyl parathion administered orally to Swiss (ICR) mice. The pesticide (purity not specified) was fed in the diet at dose levels corresponding to 0, 0.08, 0.7 or 3.0 mg/kg/day for 4 weeks. Active immunity was induced by weekly injection of vaccine (acetone-killed Salmonella typhimurium) during the period of diet treatment. Defense against microbial infection was tested by intraperitoneal injection of a single LD_{50} dose of active S. typhimurium cells. Protection by immunization was stated to be decreased in methyl parathion-treated animals, but no dose-response data were provided. The authors stated that pesticide treatment extending beyond 2 weeks was required to obtain significant increases in mortality. Increased mortality was associated with an increased number of viable bacteria in blood, decreased total gamma-globulins and specific immunoglobins in serum, and reduced splenic blast transformation in response to mitogens.

- Shtenberg and Dzhunusova (1968) studied the effect of oral exposure to methyl parathion (purity not specified) on immunity in albino rats vaccinated with NIISI polyvaccine. Three tests (six animals each) were conducted in which: (a) the vaccination was done after the animals had been on a diet supplying 1.25 mg/kg/day metaphos (methyl parathion) for 2 weeks; (b) the diet and vaccinations were initiated simultaneously; and (c) the diet was initiated 2 weeks after vaccination. The titer of agglutins in immunized control rats was 1:1,200. This titer was decreased in all exposed groups as follows: 1:46 in series (a), 1:75 in series (b) and 1:33.3 in series (c). The authors judged this to be clear evidence of inhibition of immunobiological reactivity in the exposed animals. Changes in blood protein fractions and in serum concentration of albumins were not statistically significant. Based on immune suppression, a LOAEL of 1.25 mg/kg/day was identified.

Dermal/Ocular Effects

- Gaines (1969) reported a dermal LD_{50} of 67 mg/kg for methyl parathion in male and female Sherman rats.

- Galloway (1984a,b) studied the skin and eye irritation properties of methyl parathion (technical; purity not specified) using albino New Zealand White rabbits. In the skin irritation test, 0.5 mL undiluted pesticide was applied and the treated area occluded for 4 hours. This treatment resulted in dermal edema that persisted for 24 hours, and in erythema that lasted for 6 days. After a total observation period of 9 days, a score of 2.0 was derived, and technical methyl parathion was rated as a weak irritant. In the eye irritation test, 0.1 mL of the undiluted pesticide was applied to nine eyes. Three were washed after exposure, and six were left unwashed. Conjunctival irritation was observed starting at 1 hour and lasting up to 48 hours postexposure. Maximum average irritation scores of 11 and 10.7 were assigned for nonwashed and washed eyes, respectively, and technical methyl parathion was considered a weak irritant.

- Galloway (1985) used guinea pigs to examine the sensitizing potential of methyl parathion (technical; purity not stated). Ten doses of 0.5 mL of a 10% solution (w/v in methanol) were applied to the clipped intact skin of 10 male guinea pigs (albino Hartley strain) over a 36-day period. This corresponds to an average dose of 13.9 mg/kg/day. Another group was treated with 2,4-dinitrochlorobenzene as a positive control. No skin sensitization reaction was observed in methyl parathion-treated animals.

- Skinner and Kilgore (1982) studied the acute dermal toxicity of methyl parathion in male Swiss-Webster mice, and simultaneously determined ED_{50} values for cholinesterase and acetylcholinesterase inhibition. Methyl parathion (analytical grade, 99% pure) was administered in acetone solution to the hind feet of the mice; the animals were muzzled to prevent oral ingestion through grooming. The dermal LD_{50} was 1,200 mg/kg. The ED_{50} was 950 mg/kg for cholinesterase inhibition and 550 mg/kg for acetylcholinesterase inhibition.

Long-term Exposure

- Daly and Rinehart (1980) conducted a 90-day feeding study of methyl parathion (93.65% pure) using Charles River CD-1 mice. Groups of 15 mice of each sex were given diets containing the pesticide at levels of 0, 10, 30 or 60 ppm. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to doses of about 0, 1.5, 4.5 or 9.0 mg/kg/day. All mice survived the test. Mean body weights were significantly ($p < 0.05$) depressed for both sexes at 60 ppm throughout the study and for males during the first 5 weeks at 30 ppm. Animals of both sexes had a slight but not significant ($p < 0.05$) increase in the mean absolute and relative brain weights at 60 ppm. There were dose-related decreases ($p < 0.05$) in the mean absolute and relative testes weights of all treated males and in the ovary weights of the females at 30 and 60 ppm. Gross and microscopic examination revealed no dose-related effects. Histological examination revealed no findings in the brain, testes or ovary to account for the observed changes in the weights of these organs. Measurements on ChE were not performed. Based on decreased testes weight, the LOAEL for this study was 10 ppm (1.5 mg/kg/day).

- Tegeris and Underwood (1978) investigated the toxicity of methyl parathion (94.32% a.i.) in beagle dogs fed the pesticide for 90 days at dose levels of 0, 0.3, 1.0 or 3.0 mg/kg/day. Four dogs (4-months old, 4.5 to 8.0 kg) of both sexes were used at each dose level. Soft stools were observed in all treatment groups throughout, and there was also occasional spontaneous vomiting. There were no persistent significant ($p < 0.05$) effects on body weight gain, feed intake, fasting blood sugar, BUN, SGPT, SGOT, hematological, or urological indices. Organ weights were within normal limits, with the exception of pituitary weights of females at 3.0 mg/kg, which were significantly ($p < 0.05$) higher than the control values. Gross and microscopic examination revealed no compound-related abnormalities. Plasma ChE was significantly ($p < 0.05$) depressed in both sexes at 6 and 13 weeks at 3 mg/kg/day, and in the males only at 1.0 mg/kg/day at 13 weeks; erythrocyte ChE was also significantly ($p < 0.05$) depressed in all animals at 6 and 13 weeks at 3 mg/kg/day, and in both sexes at 13 weeks at 1.0 mg/kg/day; brain ChE was significantly ($p < 0.05$) depressed in both sexes at 3.0 mg/kg/day. Based on ChE depression, the NOAEL and LOAEL for this study were identified as 0.3 mg/kg/day and 1.0 mg/kg/day, respectively.

- Ahmed et al. (1981) conducted a 1-year feeding study in beagle dogs. Methyl parathion (93.6% pure) was administered in the diet at ingested dose levels of 0, 0.03, 0.1 or 0.3 mg/kg/day. Eight animals of each sex were included at each dose level, with no overt signs of toxicity noted at any dose. There were no treatment-related changes in food consumption or body weight. Cholinesterase determinations in plasma, red blood cells and brain revealed marginal variations, but the changes were not consistent and were judged by the authors to be unrelated to dosing. Organ weight determinations showed changes in both males and females at 0.1 and 0.3 mg/kg/day, but the changes were neither dose-related nor consistent. It was concluded that there was no demonstrable toxicity of methyl parathion fed to the dogs at these levels. The NOAEL for this study was 0.3 mg/kg/day.

- NCI (1978) conducted a 2-year feeding study of methyl parathion (purity not specified) in F344 rats (50/sex/dose) at dose levels of 0, 20 or 40 ppm in the diet. Assuming that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this is equivalent to dose levels of about 0, 1 or 2 mg/kg/day. Cholinesterase levels were not measured, but no remarkable clinical signs were noted, and no significant ($p < 0.05$) changes were observed in mortality, body weight, gross pathology or histopathology. Based on this, a NOAEL of 40 ppm (2 mg/kg/day) was identified in rats.

- NCI (1978) conducted a chronic (105-week) feeding study in B6C3F$_1$ mice (50/sex/dose). Animals were initially fed methyl parathion (94.6% pure) at dose levels of 62.5 or 125 ppm. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to doses of about 9.4 or 18.8 mg/kg/day. Because of severely depressed body weight gain in males, their doses were reduced at 37 weeks to 20 or 50 ppm, and the time-weighted averages were calculated to be 35 or 77 ppm. This corresponds to doses of about 5.2 or 11.5 mg/kg/day, respectively. Females were fed at the original levels throughout. Mortality was significantly ($p < 0.05$) increased only in female mice at 125 ppm. Body weights were lower ($p < 0.05$) for both sexes throughout the test period and decreases were dose-related. No gross or histopathologic changes were noted, and ChE activity was not measured. Based on body weight, this study identified a LOAEL of 35 ppm (5.2 mg/kg/day) in male mice.

- Daly et al. (1984) conducted a chronic feeding study of methyl parathion (93.65% active ingredient) in Sprague-Dawley (CD) rats (60/sex/dose) at dose levels of 0, 0.5, 5 or 50 ppm in the diet. Using food intake/body weight data given in the study report, these levels approximate doses of about 0, 0.025, 0.25 or 2.5 mg/kg/day. At 24 months, five animals of each sex were sacrificed for qualitative and quantitative tests for neurotoxicity. Ophthalmoscopic examinations were conducted on females at 3, 12 and 24 months and terminally. Hematology, urinalysis and clinical chemistry analyses were performed at 6, 12, 18 and 24 months. Mean body weights were reduced ($p < 0.05$) throughout the study for both sexes at 50 ppm. At this dose level, food consumption was elevated ($p < 0.05$) for males during weeks 2 to 13, but reduced for females for most of the study. Hemoglobin, hematocrit and RBC count were significantly ($p < 0.05$) reduced for females at 50 ppm at 6, 12, 18 and 24 months. For males at 5 and 50 ppm at 24 months, hematocrit and RBC count were significantly ($p < 0.05$) reduced and hemoglobin was reduced, but not significantly ($p < 0.05$). At 50 ppm, plasma and erythrocyte ChE were significantly ($p < 0.05$) depressed for both sexes during the test, and brain ChE was significantly ($p < 0.05$) decreased at termination. Slight decreases in ChE activity were also observed in animals at 5 ppm, but these changes were not statistically significant ($p > 0.05$). For males, the absolute weight and the ratio to brain weight of the testes, kidneys and the liver were reduced by 10 to 16% (not significant, $p > 0.05$) in both the 5- and 50-ppm groups, while for females absolute and organ/body weights for the brain and heart (also heart/brain weight) were found to be elevated significantly ($p < 0.05$) at the same dose levels. Overt signs of cholinergic toxicity (such as alopecia, abnormal gait and tremors) were observed in the 50-ppm animals and in one female at 5 ppm. At 24 months, 15 females were observed to have retinal degeneration. There was also a dose-related occurrence of retinal posterior subcapsular cataracts, possibly related or secondary to the retinal degeneration, since 5 of the 10 cataracts occurred in rats with retinal atrophy. The incidence of retinal atrophy was 20/55 at 50 ppm, 1/60 at 5 ppm, 3/60 at 0.5 ppm and 3/59 in the control group. Examination of the sciatic nerve and other nervous tissue from five rats per sex killed at week 106 gave evidence of peripheral neuropathy (abnormal fibers, myelin corrugation, myelin ovoids) in both sexes at 50 ppm ($p < 0.05$). Too few fibers were examined at the lower doses to perform statistical analyses, but the authors stated that nerves from both sexes in low- and mid-dose groups could not be distinguished qualitatively from controls. Slightly greater severity of nerve changes found in two males was not clearly related to treatment. No other lesions were observed that appeared to be related to ingestion of methyl parathion. Based on hematology, body weight, organ weights, clinical chemistry, retinal degeneration and cholinergic signs, a NOAEL of 0.5 ppm (0.025 mg/kg/day) was identified in this study.

Reproductive Effects

- Lobdel and Johnston (1964) conducted a three-generation study in Charles River rats. Each parental dose group included 10 males and 20 females. The investigators incorporated methyl parathion (99% pure) in the diet of males and females at dose levels of 0, 10 or 30 ppm, except for reduction of each dose by 50% during the initial 3 weeks of treatment, to produce dose equivalents of 0, 1.0 and 3.0 mg/kg/day, respectively. There was no pattern with respect to stillbirths, although the 30-ppm groups had a higher total number of stillborn. Survival was reduced in weanlings of the F_{1a}, F_{1b} and F_{2a} groups at 30 ppm, and in weanlings of the F_{3a} group at 10 ppm. At 30 ppm, there was also a reduction in fertility of the F_{2b} dams at the second mating; the first mating resulted in 100% of the animals having litters, while at the second mating, only 41% had litters. Animals exposed to 10 ppm methyl parathion did not demonstrate significant deviations from the controls. A NOAEL of 10 ppm (1.0 mg/kg/day) was identified in this study.

- Daly and Hogan (1982) conducted a two-generation study of methyl parathion (93.65% pure) toxicity in Sprague-Dawley rats. Each parental dose group consisted of 15 males and 30 females. The compound was added to the diet at levels of 0, 0.5, 5.0 or 25 ppm. Using compound intake data from the study report, equivalent dose levels are about 0, 0.05, 0.5 or 2.5 mg/kg/day. Feeding of the diet was initiated 14 weeks prior to the first mating and then continued for the remainder of the study. Reduced body weight ($p < 0.05$) was observed in F_0 and F_1 dams at the 25-ppm dose level. A slight decrease in body weight was noted in F_{1a} and F_{2a} pups in the 25-ppm group, but this was not significant ($p > 0.05$). Overall, the authors concluded that there was no significant ($p > 0.05$) effect attributable to methyl parathion in the diet. Based on maternal weight gain, the NOAEL for this study was 5.0 ppm (0.5 mg/kg/day).

Developmental Effects

- Gupta et al. (1985) dosed pregnant Wistar-Furth rats (10 to 12 weeks of age) with methyl parathion (purity not specified) on days 6 to 20 of gestation. Two doses were used: 1.0 mg/kg (fed in peanut butter) or 1.5 mg/kg (administered by gavage in peanut oil). The low dose produced no effects on maternal weight gain, caused no visible signs of cholinergic toxicity and did not result in increased fetal resorptions. The high dose caused a slight but significant ($p < 0.05$) reduction in maternal weight gain (11% in exposed versus 16% in controls, by day 15) and an increase in late resorptions (25% versus 0%). The high dose also resulted in cholinergic signs (muscle fasciculation and tremors) in some dams. Acetylcholesterase (AChE) activity, choline acetyltransferase (CAT) activity, and quinuclidinyl benzilate (QNB) binding to muscarinic receptors were determined in several brain regions of fetuses at 1, 7, 14, 21 and 28 days postnatal age, and in maternal brain at day 19 of gestation. Exposure to 1.5 mg/kg reduced ($p < 0.05$) the AChE and increased CAT activity in all fetal brain regions at each developmental period and in the maternal brain. Exposure to 1.0 mg/kg caused a significant ($p < 0.05$) but smaller and less persistent reduction of AChE activity in offspring, but no change in brain CAT activity. Both doses reduced QNB binding in maternal frontal cortex ($p < 0.05$), but did not alter the postnatal pattern of binding in fetuses. In parallel studies, effects on behavior (cage emergence, accommodated locomotor activity, operant behavior) were observed to be impaired in rats exposed prenatally to 1.0 mg/kg, but not to the 1.5-mg/kg dose. No morphological changes were observed in hippocampus or cerebellum. It was concluded that subchronic prenatal exposure to methyl parathion altered postnatal development of cholinergic neurons and caused subtle alterations in selected behaviors of the offspring. The fetotoxic LOAEL for this study was 1.0 mg/kg.

- Gupta et al. (1984) administered oral doses of 1.0 or 1.5 mg/kg/day of methyl parathion (purity not specified) to female Wistar-Furth rats on days 6 through 15 or on days 6 through 19 of gestation. Protein synthesis in brain and other tissues was measured on day 15 or day 19 by subcutaneous injection of radioactive valine. The specific activity of this valine in the free amino acid pool and protein-bound pool (measured 0.5, 1.0 and 2.0 hours after injection) was significantly ($p < 0.05$) reduced in various regions of the maternal brain and in maternal viscera, placenta and whole embryos (day 15), and in fetal brain and viscera (day 19). The inhibitory effect of methyl parathion on protein synthesis was dose dependent, greater on day 19 than on day 15 of gestation and more pronounced in fetal than in maternal tissues. With respect to protein synthesis in both maternal and fetal tissues, the LOAEL of this study was 1.0 mg/kg.

- Fuchs et al. (1976) reported a study in which oral administration of methyl parathion to pregnant Wistar rats on either days 5 to 9, 11 to 15, or 11 to 19 of gestation resulted in growth retardation of offspring and increased resorptions at 3 mg/kg. The NOAEL was 1 mg/kg.

Mutagenicity

- Van Bao et al. (1974) examined the lymphocytes from 31 patients exposed to various organophosphate pesticides for indications of chromosome aberrations. Five of the examined patients had been exposed to methyl parathion. Blood samples were taken 3 to 6 days after exposure and again at 30 and 180 days. A temporary, but significant ($p < 0.05$) increase was found in the frequency of chromatid breaks and stable chromosome-type aberrations in acutely intoxicated persons. Two of the methyl parathion-exposed persons were in this category, having taken large doses orally in suicide attempts. The authors concluded that the results of this study strongly suggest that the organic phosphoric acid esters exert direct mutagenic effects on chromosomes.

- Shigaeva and Savitskaya (1981) reported that metophos (methyl parathion) induced visible morphological mutations and biochemical mutations in Pseudomonas aeruginosa at concentrations between 100 and 1,000 ug/mL, and significantly ($p < 0.05$) increased the reversion rate in Salmonella typhimurium at concentrations between 5 and 500 ug/mL.

- Grover and Malhi (1985) examined the induction of micronuclei in bone marrow cells of Wistar male rats that had been injected with methyl parathion at doses between one-third and one-twelfth of the LD_{50}. The increase in micronuclei formation led the authors to conclude that methyl parathion has high mutagenic potential.

- Mohn (1973) concluded that methyl parathion was a probable mutagen, based on the ability to induce 5-methyltryptophan resistance in Escherichia coli. Similar results were obtained using the streptomycin-resistant system of E. coli and the trp-conversion system of Saccharomyces cerevisiae.

- Rashid and Mumma (1984) found methyl parathion to be mutagenic to S. typhimurium strain TA100 after activation with rat liver microsomal and cytosolic enzymes.

- Chen et al. (1981) investigated sister-chromatid exchanges (SCE) and cell-cycle delay in Chinese hamster cells (line V79) and two human cell lines (Burkitt lymphoma B35M and normal human lymphoid cell Jeff), and found methyl parathion to be the most active pesticide of eight tested with respect to its induction potential.

- Riccio et al. (1981) found methyl parathion to be negative in two yeast assay systems (diploid strains D3 and D7 of Saccharomyces cerevisiae), based on mitotic recombination (in D3), and mitotic crossing over, mitotic gene conversion, and reverse mutation (in D7).

- In a study for dominant lethality in mice by Jorgenson et al. (1976), males (20 per dose group) were given methyl parathion in the diet for 7 weeks at 3 dose levels (not reported). Positive controls given triethylene melamine and untreated controls were also studied. Following treatment, each male was mated to 2 adult females weekly for 8 weeks. Methyl parathion was ineffective in this test.

Carcinogenicity

- NCI (1978) conducted chronic (105-week) feeding studies of methyl parathion in F344 rats and $B6C3F_1$ mice (50/sex/dose). Rats were fed methyl parathion (94.6% pure) at dose levels of 0, 20 or 40 ppm (equivalent to doses of 0, 1 or 2 mg/kg/day). Mice were initially fed dose levels of 62.5 or 125 ppm, but because of severely depressed body weight gain in males, their doses were reduced at 37 weeks to 20 or 50 ppm, respectively. Time-weighted averages for males were calculated to be 35 or 77 ppm (about 5.2 or 11.5 mg/kg/day). Females received the original dose level throughout. Based on gross and histological examinations, no tumors were observed to occur at an incidence significantly higher than that of the control value in either the mice or rats. The authors concluded that methyl parathion was not carcinogenic in either species under the conditions of the test.

- Daly et al. (1984) fed Sprague-Dawley rats (60/sex/dose) methyl parathion (93.65%) in the diet for 2 years. Doses tested were 0, 0.5, 5 or 50 ppm, estimated as equivalent to doses of 0, 0.025, 0.25 or 2.5 mg/kg/day. There were no significant ($p > 0.05$) increases in neoplastic lesions between treated and control groups.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were located in the available literature that were suitable for deriving a One-day HA value. It is recommended that the Ten-day HA value for the 10-kg child (0.3 mg/L calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The studies by Rider (1969, 1970, 1971) have been selected to serve as the basis for calculation of the Ten-day HA for methyl parathion. In these studies, human volunteers ingested methyl parathion for 30 days at doses ranging from 1 to 30 mg/day. The most sensitive indicator of effects was inhibition of plasma ChE. No effects in any subject were observed at a dose of 22 mg/day (about 0.31 mg/kg/day with assumed 70-kg body weight), and this was identified as the NOAEL. Doses of 24 mg/day inhibited ChE activity in plasma and red blood cells in two of five subjects, maximum decreases being 23 and 24% in plasma and 27 and 55% in red blood cells. Higher doses (26 to 30 mg/day) caused greater inhibition. On this basis, 24 mg/day (0.34 mg/kg/day) was identified as the LOAEL. Short-term toxicity or teratogenicity studies in animals identified LOAEL values of 1.0 to 2.5 mg/kg/day (Gupta et al., 1984, 1985; Shtenberg and Dzhunusova, 1968; Tegeris and Underwood, 1977), but did not identify a NOAEL value.

Using a NOAEL of 0.31 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.31\ \text{mg/kg/day})\ (10\ \text{kg})}{(10)\ (1\ \text{L/day})} = 0.31\ \text{mg/L}\ (300\ \text{ug/L})$$

where:

0.31 mg/kg/day = NOAEL, based on absence of toxic effects or inhibition of ChE in humans exposed orally for 30 days.

10 kg = assumed body weight of a child.

10 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from a study in humans.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The 90-day feeding study in dogs by Tegeris and Underwood (1978) has been selected to serve as the basis for calculation of the Longer-term HA for methyl parathion. In this study, a NOAEL of 0.3 mg/kg/day was identified, based on absence of effects on body weight, food consumption, clinical chemistry, hematology, urinalysis, organ weights, gross pathology, histopathology and ChE activity. The LOAEL, based on ChE inhibition, was 1.0 mg/kg/day. These values are supported by the results of Ahmed et al. (1981), who identified a NOAEL of 0.3 mg/kg/day in a 1-year feeding study in dogs, and by the study of Daly and Rinehart (1980), which identified a LOAEL of 1.5 mg/kg/day (based on decreased testes weight) in a 90-day feeding study in mice.

Using a NOAEL of 0.3 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.3\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.03\ \text{mg/L}\ (30\ \text{ug/L})$$

where:

0.3 mg/kg/day = NOAEL, based on absence of effects on body weight, food consumption, clinical chemistry, hematology, urinalysis, organ weights, gross pathology, histopathology and ChE activity in dogs fed methyl parathion for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Using a NOAEL of 0.3 mg/kg/day, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.3\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 0.10\ \text{mg/L}\ (100\ \text{ug/L})$$

where:

0.3 mg/kg/day = NOAEL, based on absence of effects on body weight, food consumption, clinical chemistry, hematology, urinalysis, organ weights, gross pathology, histopathology and ChE activity in dogs fed methyl parathion for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption by an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in rats by Daly et al. (1984) has been selected to serve as the basis for calculation of the Lifetime HA for methyl parathion. In this study, a NOAEL of 0.025 mg/kg/day was identified, based on the absence of effects on body weight, organ weights, hematology, clinical chemistry, retinal degeneration and cholinergic signs. A LOAEL of 0.25 mg/kg/day was identified, based on decreased hemoglobin, red blood cell counts, and hematocrit (males), changes in organ-to-body weight ratios (males and females) and one case of visible cholinergic signs. There was increased retinal degeneration at 2.5 mg/kg/day, but this was not greater than control at 0.25 or 0.025 mg/kg/day. This LOAEL value (0.25 mg/kg/day) is lower than most other NOAEL or LOAEL values reported in other reports. For example, NOAEL values of 0.3 to 3.0 mg/kg/day have been reported in chronic studies by Ahmed et al. (1981), NCI (1978), Lobdell and Johnston (1964) and Daly and Hogan (1982).

Using a NOAEL of 0.025 mg/kg/day, the Lifetime HA for a 70-kg adult is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.025 \text{ mg/kg/day})}{(100)} = 0.00025 \text{ mg/kg/day}$$

where:

0.025 mg/kg/day = NOAEL, based on absence of cholinergic signs or other adverse effects in rats exposed to methyl parathion in the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.00025 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.009 \text{ mg/L } (9 \text{ ug/L})$$

where:

0.00025 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.009 \text{ mg/L}) (20\%) = 0.002 \text{ mg/L } (2 \text{ ug/L})$$

where:

0.009 mg/L = DWEL.

20% = relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenic activity was detected in either rats or mice in a 105-week feeding study (NCI, 1978).

- Statistically significant ($p < 0.05$) increases in neoplasm frequency were not found in a 2-year feeding study in rats (Daly et al., 1984).

- The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of methyl parathion.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), methyl parathion may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- NAS (1977) concluded that data were inadequate for calculation of an ADI for methyl parathion. However, using data on parathion, NAS calculated an ADI for both parathion and methyl parathion of 0.0043 mg/kg/day, using a NOAEL of 0.043 mg/kg/day in humans (Rider et al., 1969) and an uncertainty factor of 10 (NAS, 1977). From this ADI, NAS calculated a chronic Suggested-No-Adverse-Response Level (SNARL) of 0.03 mg/L, based on water consumption of 2 L/day by a 70-kg adult, and assuming a 20% RSC.

- The U.S. EPA Office of Pesticide Program (EPA/OPP) previously calculated a provisional ADI (PADI) of 0.0015 mg/kg/day, based on a NOAEL of 0.3 mg/kg/day. This is based on the 90-day dog study by Tegeris and Underwood (1978) and a 200-fold uncertainty factor. This PADI has been updated to use a value of 0.0025 mg/kg/day based on a NOAEL of 0.0250 mg/kg/day in a 2-year rat chronic feeding study and a 100-fold uncertainty factor.

- ACGIH (1984) has proposed a time-weighted average threshold limit value of 0.2 mg/m^3.

- The National Institute for Occupational Safety and Health has recommended a standard for methyl parathion in air of 0.2 mg/m^3 (TDB, 1985).

- The U.S. EPA has established residue tolerances for parathion and methyl parathion in or on raw agricultural commodities that range from 0.1 to 0.5 ppm (CFR, 1985). A tolerance is a derived value based on residue levels, toxicity data, food consumption levels, hazard evaluation and scientific judgment; it is the legal maximum concentration of a pesticide in or on a raw agricultural commodity or other human or animal food (Paynter et al., undated).

- The World Health Organization established an ADI of 0.02 mg/kg/day (Vettorazi and van den Hurk, 1985).

VII. ANALYTICAL METHODS

- Analysis of methyl parathion is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus-containing pesticides in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. The method detection limit has not been determined for methyl parathion, but it is estimated that the detection limits for analytes included in this method are in the range of 0.1 to 2 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) and reverse osmosis (RO) will effectively remove methyl parathion from water.

- Whittaker (1980) experimentally determined adsorption isotherms for methyl parathion and methyl parathion diazinion bi-solute solutions. As expected, the bi-solute solution showed a lesser overall carbon capacity than that achieved by the application of pure solute solution.

- Under laboratory conditions, GAC removed 99+% of methyl parathion (Whittaker et al., 1982).

- Reverse osmosis is a promising treatment method for methyl parathion-contaminated water. Chian (1975) reported 99.5% removal efficiency for two types of membrane operating at 600 psig and a flux rate of 8 to 12 gal/ft^2/day. Membrane adsorption, however, is a major concern and must be considered, as breakthrough of methyl parathion would probably occur once the adsorption potential of the membrane was exhausted.

- Oxidation with ozone and chlorine may be possible in the treatment of methyl parathion.

- Oxidation with 4.5 and 9.5 mg/L ozone reduced the methyl parathion by 95 to 99%. The same removal efficiency was achieved with 1 and 2 mg/L chlorine (Gabovich and Kurennoy, 1974).

- Ozonation with 0.32 mg ozone/mg methyl parathion reduced methyl parathion in drinking water by 90 to 95% (Shevchenko et al., 1982).

- Oxidation degradation by either ozone or chlorine produces several degradation products, whose environmental toxic impact should be evaluated prior to selecting oxidative degradation for treatment of methyl parathion-contaminated water (Shevchenko et al., 1982).

- Aeration does not seem to be a practical technique for removing methyl parathion from potable water (Saunders and Sieber, 1983).

- Treatment technologies for the removal of methyl parathion from water are available and have been reported to be effective. However, selection of individual or combinations of technologies for methyl parathion removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

IX. REFERENCES

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

METOLACHLOR

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 51218-45-2

Structural Formula

2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide

Synonyms

- o-Acetanilide; 2-chloro-6'-ethyl-N-(2-methoxy-1-methylphenyl); Dual®; Bicep®; Metetilachlor; Pimagram; Primextra; CGA-24705.

Uses (Meister, 1986)

- Selective herbicide for pre-emergence and preplant incorporated weed control in corn, soybeans, peanuts, grain sorghum, pod crops, cotton, safflower, woody ornamentals, sunflowers and flax.

Properties (Meister, 1986; Ciba-Geigy, 1977; Windholz et al., 1983; Worthing, 1983)

Chemical Formula	$C_{15}H_{22}NO_2Cl$
Molecular Weight	283.46
Physical State	White to tan liquid
Boiling Point	100°C (at 0.001 mm Hg)
Melting Point	--
Density	--
Vapor Pressure (20°C)	1.3×10^{-5} mm Hg
Specific Gravity	--
Water Solubility (20°C)	530 mg/L
Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Metolachlor has been found in 2,091 of 4,161 surface water samples analyzed and in 13 of 596 ground water samples (STORET, 1988). Samples were collected at 332 surface water locations and 551 ground water locations, and metolachlor was found in 7 states. The 85th percentile of all nonzero samples was 11.5 ug/L in surface water and 0.25 ug/L in ground water sources. The maximum concentration found was 139 ug/L in surface water and 11.0 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Metolachlor residues resulting from agricultural use have also been detected in ground water in Iowa and Pennsylvania with concentrations ranging from 0.1 to 0.4 ppb.

Environmental Fate

- ^{14}C-Metolachlor (test substance uncharacterized), at approximately 4.6 lb active ingredient (ai)/acre (A), degraded with a half-life of 48-144 hours at 39-44°C when irradiated with artificial light (uncharacterized) and 6-8 days (approximately 3,000 Langley units) at 50-55°C when irradiated with natural sunlight (Aziz, 1974). The degradate, N-propen-1-ol-2-yl-N-chloroacetyl-2-methyl-6-ethylaniline (CGA-41638), was approximately 4-6% of the applied in both the artificial light- and natural sunlight-irradiated samples; three unknown degradates were also isolated. Nonextractable ^{14}C-residues accounted for approximately 40% of the applied, and volatiles accounted for approximately 7-10% of the applied after 168 hours of irradiation with artificial light or 8 days of irradiation with natural sunlight.

- ^{14}C-Metolachlor (purity unspecified at approximately 8 ppm was essentially stable in loamy sand soil, over a period of 64 days (Kaiser, 1974). Serilization of the soil had no appreciable effect on degradation. The soil was maintained at approximately 60% of field capacity (temperature unspecified).

- ^{14}C-Metolachlor (purity unspecified) at 1-10 ppm adsorbed to sandy clay loam, loam, and two sand soils with Freundlich adsorption constants (K) ranging from 1.54 to 10 ug/g indicating mobility in these soils (Burkhard, 1978). Except for one sand soil, as soil organic matter content increased, adsorption increased. In loam soil ^{14}C-metolachlor desorbed with K values of 4.87 and 3.57 after 1 and 3 days, respectively. Adsorption and desorption occurred at about the same rate.

- Aged (30 days) ^{14}C-Metolachlor (purity unspecified) residues were mobile in columns of loamy sand soil with approximately 26% of applied radioactivity leached from the columns, and approximately 87% of the applied radioactivity remaining in the soil (Dupre, 1974a). Radioactivity was concentrated (approximately 60% of applied) in the top 3 inches of soil.

- ^{14}C-Metolachlor (purity unspecified) residues were mobile in sandy loam, sand, and silt loam soils (detected to the 12-inch depth in 12-inch columns) when leached with 20 inches of water (Houseworth, 1973?). ^{14}C-Metolachlor residues were immobile in peat soil with approximately 98.8% of the applied radioactivity detected in the top 1 inch of soil. The leachate from the sandy loam, sand, loam, and silt loam soils contained 36.4, 20.9, 4.0, and 0.4% of the applied radioactivity, respectively.

- ^{14}C-Metolachlor (purity unspecified) residues at 1 lb ai/A dissipated from a loamy sand soil (8° slope) in the leachate (0.25% of applied radioactivity), and the runoff water (3.15% of applied) and sediment (1.41% of applied) after the application of approximately 1.52 inches of simulated rainfall in 7 days (Dupre, 1974b). Of the applied rainfall, approximately 85% was collected as runoff. Greater than 85% and 5% of the applied radioactivity was detected in the treated and untreated soils, respectively. Total recovery of radioactivity was 95.8% of applied.

- Freundlich adsorption K values of 0.58, 1.46, and 7.83 were calculated for ^{14}C-metolachlor (test substance uncharacterized) in sand, silt loam, and sandy loam soils, respectively (Harvey and Jordan, 1978). Adsorption was positively correlated to soil organic matter content.

- Lettuce planted 14 weeks posttreatment and harvested at 26 weeks contained 0.025 ppm of ^{14}C-metolachlor residues (Newby, 1979). Lettuce planted 41 weeks posttreatment and sampled at 13 and 15 weeks contained 0.144 and 0.065 ppm of ^{14}C-metolachlor residues, respectively. Soil at about 40 and 56 weeks posttreatment cotained approximately 70-80 and 95% nonextractable ^{14}C-metolachlor residues, respectively.

- Residues of phenyl-labeled ^{14}C-metolachlor were taken up by greenhouse-grown, rotational winter wheat planted 168 days after a 2.0 lb ai/A application to a silt loam soil (Sumner and Cassidy, 1974d). Total radioactivity was <0.15 ppm in forage sampled 189 to 238 days posttreatment, and 0.60 and 0.03 ppm in straw and grain, respectively, harvested 273 days posttreatment.

- Residues of phenyl-labeled ^{14}C-metolachlor were taken up by greenhouse-grown, rotational oats planted 270 days after a 2.0 lb ai/A application to a silt loam soil (Sumner and Cassidy, 1974c). Total radioactivity was <0.17 ppm in forage sampled 300-330 days posttreatment, and 0.27 and 0.05 ppm in straw and grain, respectively, harvested 375 days posttreatment.

- ^{14}C-Metolachlor residues were detected in the whole plant (0.04 ppm), tops (<0.09 ppm), and roots (<0.06 ppm) of rotational carrots planted 9 months after an application of ^{14}C-metolachlor (purity unspecified) at 2 lb ai/A to silt loam soil (Sumner and Cassidy, 1974a). Total residues of ^{14}C-metolachlor in the silt loam soil were 0.26 ppm in the 0-3 inch depth at carrot planting, and 0.04-0.35 ppm in the 0-9 inch profile in the subsequent samplings through harvest.

- ^{14}C-Metolachlor residues were detected in the whole plant (<0.17 ppm), stalks (0.07 ppm), beans (0.04 ppm), meal (0.05 ppm), and oil (<0.01 ppm) of rotational soybeans planted 9 months after an application of ^{14}C-metolachlor (purity unspecified) at 2 lb ai/A to silt loam soil

(Sumner and Cassidy, 1974b). Total residues of ^{14}C-metolachlor in the silt loam soil were 0.26 ppm in the 0-3 inch depth at soybean planting, and 0.06-0.35 ppm in the 0-9 inch profile in the subsequent samplings through harvest.

- Photodegradation studies in water: One study (Aziz and Kahrs, 1974; Aziz and Kahrs, 1975) cannot be validated because the experimental conditions were referenced, rather than described, and the reference was not available for review. In addition, this study would not fulfill data requirements because the test substance was uncharacterized, the incubation temperatures were not reported, it was not reported if the test solutions were buffered or if wavelengths <290 nm were filtered out, the conditions under which dark controls were maintained were not reported, the natural sunlight conditions were not provided, the intensity and wavelength distribution of the artificial light source were not provided, and degradates that comprised >10% of the applied that were detected in the test solution exposed to artificial light were not characterized.

- Leaching and adsorption/desorption studies: Four studies were reviewed and considered to be scientifically valid. The first study (Burkhard, 1978) partially fulfills data requirements by providing information on the adsorption of parent metolachlor. However, the study was not conducted in a 0.01 N calcium ion solution, desorption data were reported for only one of the four soils tested, and the majority of the study was conducted on foreign soils. The second study (Dupre, 1974a) partially fulfills data requirements by providing information on the mobility of aged (30 days) metolachlor residues. However, the purity of the test substance was unspecified, K_d values were not reported, and ^{14}C-metolachlor residues were not characterized. The third study (Houseworth, 1973a) partially fulfills data requirements by providing information on the mobility of metolachlor residues. However, the purity of the test substance was unspecified, and K_d values were not reported. The fourth study (Harvey and Jordan, 1978) partially fulfills data requirements by providing information on the adsorption of parent metolachlor. However, the test substance was uncharacterized, and the study was not conducted in a 0.01 N calcium ion solution.

- Ground and surface water monitoring studies: Submitted data indicate that metolachlor is mobile in soil (Burkhard, 1978; Houseworth, 1973?) and available in surface water runoff (Dupre, 1974b). Monitoring data (Ross and Balu, 1985) indicate metolachlor is present in surface waters.

III. PHARMACOKINETICS

Absorption

- In studies conducted by Hambock (1974a,b), rats were administered a single oral dose (28.6 or 52.4 mg/kg) of metolachlor (purity not specified, but ^{14}C-labeled and unlabeled metolachlor were synthesized for these experiments). The chemical was readily absorbed, since 70 to 90% of the metolachlor was excreted as metabolites within 48 hours.

Distribution

° Data from rats given radioactive metolachlor (approximately 3.2 to 3.5 mg/kg) orally demonstrated that the chemical is rapidly metabolized. Residues in meat tissues and blood were very low and only blood contained residue levels in excess of 0.1 ppm (Hambock, 1974c).

Metabolism

° Studies conducted to identify urinary and fecal metabolites in the rat indicated that metolachlor is metabolized via dechlorination, O-methylation, N-dealkylation and side-chain oxidation (Hambock, 1974 a,b). Urinary metabolites included 2-ethyl-6-methylhydroxyacetanilide (MET-002) and N-(2-ethyl-6-methylphenyl)-N-(hydroxyacetyl)-DL-alanine) (MET-004). Fecal metabolites included 2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-hydroxy-1-methylethyl) (MET-003) and MET-004.

Excretion

° When treated with ^{14}C-metolachlor (approximately 31 mg/kg orally), male rats excreted 21.5% and 51.4% of the administered dose in the urine and feces, respectively, in 48 hours (Hambock, 1974a,b). The excreta contained 1, 15 and 22% of the administered dose as MET-002, MET-003 and MET-004, respectively. No unchanged chemical was isolated, and no glucuronide or sulfate conjugates were identified.

IV. HEALTH EFFECTS

Humans

° Signs of human intoxication from metolachlor and/or its formulations (presumably following acute deliberate or accidental exposures) include abdominal cramps, anemia, ataxia, dark urine, methemoglobinemia, cyanosis, hypothermia, collapse, convulsions, diarrhea, gastrointestinal irritation, jaundice, weakness, nausea, shock, sweating, vomiting, CNS depression, dizziness, dyspnea, liver damage, nephritis, cardiovascular failure, skin irritation, dermatitis, sensitization dermatitis, eye and mucous membrane irritation, corneal opacity and adverse reproductive effects (HAZARDLINE, 1985).

Animals

Short-term Exposure

° The acute oral LD_{50} of technical metolachlor in the rat was reported to be 2,780 mg/kg (95% confidence range of 2,180 to 3,545 mg/kg; Bathe, 1973).

° Technical metolachlor in corn oil was shown to be emetic in beagle dogs, precluding the establishment of an LD_{50} (Roche, 1974). However, an "emetic dose" of 19 ± 9.7 mg/kg was established.

- Beagle dogs were fed technical metolachlor in the diet for 7 days in a range-finding study (Goldenthal et al., 1979). Each test group consisted of one male and one female. Doses were 1,000, 3,000 or 5,000 ppm with the controls receiving a basic diet plus the test material solvent (ethanol). The mean doses were 0, 13.7, 22.7 or 40.2 mg/kg. Decreased food consumption and body weight indicated that the two higher doses were unpalatable. No changes were observed at the lowest dose, although the animals exhibited soft stools and/or diarrhea over the study period. No other signs of overt toxicity, morbidity or mortality were observed in any animal. Accordingly, the lowest dose (13.7 mg/kg) is the No-Observed-Adverse-Effect Level (NOAEL) in this study.

Dermal/Ocular Effects

- The LD_{50} of technical metolachlor in the rabbit when tested by the unabraded dermal route is greater than 10,000 mg/kg (Bach, 1974).

- Sachsse (1973b) evaluated the dermal irritation potential of technical metolachlor (3/sex/dose) on the Russian strain rabbits (weighing 2 to 3 kg). The chemical was applied to abraded and unabraded skin for 24 hours and then observed for periods up to 72 hours. The results demonstrated that technical metolachlor is non-irritating to rabbit skin.

- Sachsse and Ullman (1977) studied skin sensitization in the albino guinea pig by the intradermal-injection method. Technical metolachlor (CG-24705) dissolved in the vehicle (propylene glycol) and the vehicle alone were intradermally injected into the skin of two groups of Pilbright guinea pigs. A positive reaction was observed in the animals injected with metolachlor in vehicle, but not in animals treated with the vehicle alone. The authors concluded that technical metolachlor is a skin sensitizer.

- A study of eye irritation by technical metolachlor in the Russian strain rabbit (3/sex/dose) was conducted by Sachsse (1973a). The chemical was applied at a dose level of 0.1 mL/eye. Evaluation of both washed and unwashed eyes 24 hours and 7 days later revealed no evidence of irritation.

Long-term Exposure

- Beagle dogs (four/sex/dose) were administered technical metolachlor (>90% ai) in their feed for up to 15 weeks (Coquet et al., 1974). Initial doses were 0, 50, 150 or 500 ppm (equivalent to 0, 4 to 5, or 14 to 19 mg/kg/day). However, after 8 weeks, the group receiving 50 ppm was switched to a diet that delivered 1,000 ppm (27 to 36 mg/kg/day) for the remaining 6 weeks. The dose was increased because no signs of toxicity were observed in the 500-ppm group after 8 weeks. No animals died during the study and no significant changes were observed in gross or histological pathology, blood or urine analyses. Except for a decrease in food consumption and associated slight weight loss at the 1,000-ppm dose, no compound-related effects were observed. The NOAEL for this study is 500 ppm (14 to 19 mg/kg/day).

- Tisdel et al. (1982) presented the results of a study in which metolachlor (95% ai) was administered to Charles River CD-1 mice (68/sex/dose) for 2 years at dietary concentrations of 0, 300, 1,000 or 3,000 ppm. Time-Weighted Average (TWA) concentrations, based upon diet analyses, were equal to 0, 287, 981 and 3,087 ppm. The dietary doses, from reported food intake and body weight data, were calculated to be equal to 0, 50, 170 or 526 mg/kg/day for the males and 0, 64, 224 or 704 mg/kg/day for the females. No treatment-related effects were observed in terms of physical appearance, food consumption, hematology, serum chemistry, urinalysis or gross or histopathology. However, mortality was increased significantly in females fed 3,000 ppm (704 mg/kg/day). Statistically significant reductions in body weight gain were observed in both sexes at the highest dose. Also, statistically significant changes in absolute and organ-to-body weight ratios were noted occasionally (e.g., kidney- and liver-body weight ratios and decreased seminal vesicle to body weight ratio in high dose males). Based on this information, a NOAEL of 1,000 ppm (170 mg/kg/day for males and 224 mg/kg/day for females) is identified.

- Tisdel et al. (1983) presented the results of a study in which metolachlor (purity not specified) was administered to CD-Crl:CD (SD) BR rats for 2 years at dietary concentrations of 0, 30, 300 or 3,000 ppm. Assuming that 1 ppm in the diet of rats is equal to 0.05 mg/kg/day (Lehman, 1959), these dietary concentrations would be equal to 0, 1.5, 15 or 150 mg/kg/day. The control and 3,000-ppm groups consisted of 70 rats/sex. The 30- and 300-ppm groups consisted of 60 rats/sex. No treatment-related effects were noted in terms of mortality, organ weight and organ-to-body weight ratios. A variety of differences in clinical pathology measurements was found between control and treatment groups at various time intervals, but no consistent dose-related effects were apparent with the exception of a decrease in glutamic-oxaloacetic transaminase activity in high dose males at 12 months, the significance of which is uncertain. Mean body weights of high-dose females were consistently less than controls from week 2 until termination of the study. This difference was statistically significant ($p < 0.01$) for 26 of the 59 intervals at which such measurements were made. Food consumption in high-dose females also was generally less than controls. Gross pathology findings were described by the investigators as being unremarkable. Based on this data, a NOAEL of 300 ppm (15 mg/kg/day) is identified.

Reproductive Effects

- A three-generation rat reproduction study was reported by Adler and Smith (1978). Targeted dietary exposures for metolachlor (96.5% ai) were 0, 30, 300 or 1,000 ppm. The actual exposures were analyzed to be 0, 30, 250 or 850 ppm. Assuming that 1 ppm equals 0.05 mg/kg/day (Lehman, 1959), the doses were calculated to be 0, 1.5, 22.5 or 42.5 mg/kg bw/day. No adverse effects were noted at any dose. A minimal NOAEL of 42.5 mg/kg is identified for reproductive effects.

- Smith et al. (1981) conducted a two-generation reproduction study in which Charles River CD rats (15 males and 30 females/dose) were administered technical-grade metolachlor (purity not specified) at dietary doses of 0, 30, 300 or 1,000 ppm. The TWA concentrations of metolachlor, based upon dietary analysis, were 0, 32, 294 or 959 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these dietary concentrations are approximately equal to 0, 1.6, 14.7 or 48 mg/kg/day. Mating, gestation, lactation, and female and male fertility indices were not affected in either generation. Additionally, pup survival was not affected. However, pup weights in the 959-ppm dose group, but not the 32- and 294-ppm dose groups, were significantly reduced in the F_{1a} and F_{2a} litters. Food consumption was reduced significantly for F_1 females receiving 32 ppm (1.6 mg/kg/day) and greater at various study intervals. Other effects that appeared to be treatment-related included increased liver-to-body weight ratios for both F_1 parental males and females at 1,000 ppm and increased thyroid-to-body weight and thyroid-to-brain weight in F_1 males at 1,000 ppm. Based on reduced pup weights, a reproductive NOAEL of 294 ppm (14.7 mg/kg/day) is identified.

- Tisdel et al. (1980) gave metolachlor (95% ai) to CD-1 mice (68/sex/dose) in the food for 2 years at concentrations of 0, 300, 1,000 or 3,000 ppm (the TWAs based on diet analyses were 0, 287, 981 or 3,087 ppm and corresponded to 0, 50, 170 or 520 mg/kg/day in males and to 0, 64, 224 or 704 mg/kg/day in the females). At the high dose, males were found to have a reduced seminal vesical-to-body weight ratio.

- Tisdel et al. (1983) exposed CD-Crl:CD (SD) BR rats (70/sex/dose) to metolachlor (purity not specified) in the diet for 2 years at 0, 30, 300 or 3,000 ppm (the doses correspond to 0, 1.5, 15 or 150 mg/kg/day). They observed greater testicular atrophy and degeneration of the tubular epithelium in the 300- and 3,000-ppm groups than in the control group.

Developmental Effects

- Fritz (1976) conducted a rat teratology study in which pregnant females (25/dose level) were administered doses of technical metolachlor (purity not specified) orally at 0, 60, 180 or 360 mg/kg/day during days 6 to 15 of gestation. No fetotoxic or developmental effects were noted.

- Lightkep et al. (1980) evaluated the teratogenic potential of metolachlor (95.4% pure) in New Zealand White rabbits (16/dose). The compound was administered via stomach tube as a suspension in aqueous 0.75% hydroxymethylcellulose at levels of 0, 36, 120 or 360 mg/kg/day. Single oral doses were given on days 6 to 18 of gestation. Abortions occurred in two rabbits: one in the 120-mg/kg/day group on day 25 (one early resorption) and one in the 360-mg/kg/day group on day 17 (one fetus) and day 20 (eight additional implantations). They did not consider these abortions to be treatment-related. Maternal toxicity (decreased food consumption and pupillary constriction) was observed in animals receiving the two highest doses. The highest dose group also exhibited blood in the cage pan and body weight loss over the treatment period. No significant developmental or fetotoxic effects were observed in the 319 fetuses, pups or late resorptions evaluated from all dose groups. Thus, a minimal NOAEL of 360 mg/kg/day for fetotoxicity and a NOAEL of 36 mg/kg/day for maternal toxicity were identified.

Mutagenicity

° Technical metolachlor (purity not specified) was tested in the Ames Salmonella test system, using S. typhimurium strains TA1535, TA1537, TA98 and TA100 (Arni and Muller, 1976). No increase in mutagenic response was observed, with or without microsomal activation, at concentrations of 10, 100, 1,000 or 10,000 ug/plate. Toxicity was observed at 1,000 and 10,000 ug/plate without activation and at 10,000 ug/plate with activation.

° Fritz (1976) reported the results of a dominant lethal study in male albino NMRI-derived mice using technical metolachlor (purity not specified). The compound was administered orally in single doses of 0, 100 or 300 mg/kg to males that then were mated to untreated females over a period of 6 weeks. No evidence of adverse effects were observed, as expressed by increased implantation loss or resorptions.

Carcinogenicity

° Marias et al. (1977) presented the results of a study in which technical-grade metolachlor was administered to Charles River CD-1 mice (50/sex/dose) at dietary concentrations of 0, 30, 300 or 3,000 ppm. Assuming that 1 ppm in the diet of the mouse is equal to 0.15 mg/kg/day (Lehman, 1959), these dietary levels are approximately 0, 4.5, 150 or 450 mg/kg/day. Males received the test material for 18 months; females received the test material for 20 months. Two samples of metolachlor (99.9% ai and 96.5% ai) were received. The 99.9% sample was used in dietary formulations for the first 33 weeks and the 96.5% pure sample was used for the rest of the study. Results of this study indicated no evidence of oncogenicity in either sex.

° Tisdel et al. (1982) presented the results of a study in which metolachlor (95% ai) was administered to Charles River CD-1 mice (68/sex/dose) for 2 years at dietary concentrations of 0, 300, 1,000 or 3,000 ppm. From food intake and body weight data, the doses were calculated to be equal to 0, 50, 170 or 526 mg/kg/day for the males and 0, 64, 224 or 704 mg/kg/day for the females. A statistically significant increase in the incidence of alveolar tumors in high-dose males was noted at the 18-month sacrifice; however, this effect was not confirmed by the final sacrifice at 24 months or by total tumor incidences for all animals.

° Ciba-Geigy (1979) reported the results of a study in which technical metolachlor was administered to Charles River albino rats in their diet for 2 years at doses equivalent to 0, 1.5, 15 or 50 mg/kg/day. A statistically significant increase in the incidence of primary liver tumors was observed in the high-dose females (15/60 compared with 5/60 at mid doses and 3/60 at the low dose and control). These tumors included hypertrophic-hyperplastic nodules, angiosarcoma, cystic cholangioma and hepatocellular carcinoma. The variety of tumor expression forms suggests that a variety of cell types and locations may be affected in the liver.

° Tisdel et al. (1983) presented the results of a study in which metolachlor (purity not specified) was administered to CD-Crl:CD (SD) BR rats for 2 years at dietary concentrations of 0, 30, 300 or 3,000 ppm. These doses were assumed to be equal to 0, 1.5, 15 or 150 mg/kg/day. An increased incidence of proliferative hepatic lesions (combined neoplastic nodules/carcinomas) was found in the high-dose females at terminal sacrifice ($p < 0.018$ by the Fisher exact test). Six of the 60 had neoplastic nodules ($p < 0.05$) and 7 of the 60 had liver tumors (one additional tumor was diagnosed as a carcinoma; $p < 0.01$).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable information was found in the available literature for determination of a One-day HA for metolachlor. Accordingly, it is recommended that the Longer-Term HA value for the 10 kg child (2.0 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

There were no satisfactory studies found in the available literature to use for the calculation of the Ten-day HA. It is, therefore, recommended that the Drinking Water Equivalent Level (DWEL), of adjusted for a 10-kg child 2 mg/L (2,000 mg/L), be used for the Ten-day HA.

Longer-Term Health Advisory

No studies were found in the literature that were suitable for deriving the Longer-term HA value for metolachlor. In the lifetime study of Tisdel et al. (1983), a NOAEL of 15 mg/kg/day was found in rats. This NOAEL was similar to that NOAEL (13.7 mg/kg/day) found by Goldenthal et al. (1979). However, Goldenthal et al. (1979) used only one dog of each sex per dose group (0, 13.7, 22.7 or 40.2 mg/kg/day), while Tisdel et al. (1983) used 70/sex/dose at 01.5, 15 or 150 mg/kg/day. Accordingly, more confidence can be placed in the Tisdel et al. study. It is, therefore, recommended that the DWEL of 5.0 mg/L (5,000 ug/L) calculated below be used for the Longer-term HA value for an adult, and that the DWEL adjusted for a 10-kg child, 2.0 mg/L (2,000 ug/L), be used for the Longer-term HA for a child.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Tisdel et al. (1983) has been selected to serve as the basis for the Lifetime HA. In this study, rats were given dietary doses of metolachlor equivalent to 0, 1.5, 15 or 150 mg/kg/day. No treatment-related effects were noted in terms of mortality, organ weight and organ-to-body weight ratios. The investigators noted a statistically significant decrease in glutamic-oxaloacetic transaminase activity in high-dose males at 12 months. Mean body weights of high-dose females were consistently less than controls from week 2 until termination of the study. This difference was significant ($p < 0.01$) for 26 of the 59 intervals at which such measurements were made. Food consumption in high-dose females also was generally less than controls. Gross pathology findings were described as unremarkable. Based on the decreased body weight gain at 3,000 ppm (150 mg/kg/day), a NOAEL of 300 ppm (15 mg/kg/day) was identified.

The Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD):

$$RfD = \frac{15 \text{ mg/kg/day}}{100} = 0.15 \text{ mg/kg/day}$$

where:

15 mg/kg/day = NOAEL, based upon the absence of systemic effects in rats exposed to metolachlor in the diet for two years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.15 \text{ mg/kg/day})(70 \text{ kg})}{(2 \text{ L/day})} = 5.25 \text{ mg/L } (5{,}000 \text{ ug/L})$$

where:

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(5.25 \text{ mg/L})\ (20\%)}{(10)} = 0.1 \text{ mg/L } (100 \text{ ug/L})$$

where:

5.25 mg/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- Four studies evaluating the carcinogenic potential of metolachlor have been identified. In two of these studies (Marias et al., 1977, and Tisdel et al., 1980), no evidence of carcinogenicity in mice was observed. The other studies, both conducted using rats, showed an increased tumor incidence related to treatment. Ciba-Geigy (1979) reported a statistically significant increase in primary liver tumors in female Charles River rats exposed to 150 mg/kg/day in the diet for 2 years. Tisdel et al. (1983) also reported a statistically significant increase in the incidence of proliferative hepatic lesions (neoplastic nodules and carcinomas) in female rats at the same dietary dose over the same time period. Additionally, there was a nonstatistically significant increase in the frequency of adenocarcinoma of the nasal turbinates and fibrosarcoma of the nasal tissue in the high-dose males (150 mg/kg/day).

- The International Agency for Research on Cancer has not evaluated the carcinogenicity of metolachlor.

- Applying the criteria described in EPA's guidelines for the assessment of carcinogenic risk (U.S. EPA, 1986a), metolachlor is classified in Group C: possible human carcinogen. This category is for substances with limited evidence of carcinogenicity in animals and absence of human data.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- EPA/OPP has identified an ADI for metolachlor of 0.015 mg/kg/day based on the NOAEL of 30 ppm (1.5 mg/kg/day) from the chronic rat feeding study (Tisdel et al., 1983) and an uncertainty factor of 100 (U.S. EPA, 1986b). Using this ADI and an assumed body weight of 60 kg, the maximum permissible intake has been calculated to be 0.9 mg/day. The total maximum residue concentration is 0.07209 mg/day or about 8% of the ADI.

- Residue tolerances ranging from 0.02 to 30 ppm have been established for a variety of agricultural products (CFR, 1985).

VII. ANALYTICAL METHODS

- Analysis of metolachlor is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using a capillary column GC. Measurement is made using a nitrogen phosphorus detector. This method has been validated in a single laboratory, and estimated detection have been determined for the methods using this method. The estimated detection limit for metolachlor is 0.75 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Whittaker (1980) experimentally determined adsorption isotherms for metolachlor on granular-activated carbon (GAC) Nuchar WV-G. Nuchar WV-G, reportedly, exhibited the following adsorption capacities at 20°C: 0.173, 0.148 and 0.105 mg metolachlor/mg carbon at concentrations of 79.84 mg/L, 10 mg/L and 1.74 mg/L, respectively.

- Holiday and Hardin (1981) reported the results of GAC treatment of wastewater contaminated with pesticides including metolachlor. The column, 3.5 ft in diameter, was packed with 10 ft of granular activated carbon, or 3,150 lb carbon/column. The column was operated at 1.04 gpm/ft^2 hydraulic load and 72 minutes contact time. Under these conditions, 99.5% of the metolachlor was removed from wastewater at an initial average concentration of 16.4 mg/L.

- GAC adsorption appears to be the most promising treatment technique for the removal of metolachlor from water. However, more actual data are required to determine the effectiveness of GAC in removing metolachlor from contaminated drinking water supplies.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August 1988

METRIBUZIN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

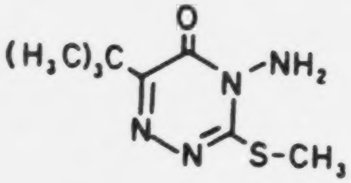
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 21087-64-9

Structural Formula



4-Amino-6-(1,1-dimethylethyl)-3-methylthio-1,2,4-triazin-5(4H)-one

Synonyms

- Bayer 6159; Bayer 6443H; Bayer 94337; Lexone; Sencor; Sencoral; Sencorer; Sencorex

Uses

- Herbicide used for the control of a large number of grass and broadleaf weeds infesting agricultural crops (Meister, 1983).

Properties (CHEMLAB, 1985)

Chemical Formula	$C_8H_{14}ON_4S$
Molecular Weight	214.28
Physical State (at 25°C)	white crystalline solid
Boiling Point	--
Melting Point	125-126°C
Density	--
Vapor Pressure (25°C)	10^{-5} mmHg (20°C)
Specific Gravity	--
Water Solubility (25°C)	1,200 mg/L
Log Octanol/Water Partition Coefficient	-5.00 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Metribuzin has been found in 936 of 4,651 surface water samples analyzed and in none of 416 ground water samples (STORET, 1988). These samples were collected at 376 surface water locations and 293 ground water locations; metribuzin was found in 14 states. The 85th percentile of all nonzero samples was 4.79 ug/L in surface water. The maximum concentration found in surface water was 34.45 ug/L.

This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Metribuzin has been found in Iowa ground water resulting from agricultural uses; typical positives were 1 to 4.3 ppb (Cohen et al., 1986).

Environmental Fate

- The rate of hydrolysis of metribuzin is pH dependent. During a 28-day test, little or no degradation was observed at pH 6 or 9 at 25°C, or at pH 6 at 37°C or 52°C (Day et al., 1976).

- ^{14}C-Metribuzin on silty clay soil degraded, with a half-life of 15 days, when exposed to natural sunlight (Khasawinah, 1972). The half-life in control samples kept in the dark was 56 days. After 10 weeks, 20.6, 6.5 and 7.0% of the applied radioactivity was present in the irradiated soil as 6-t-butyl-1,2,4-triazin-3,5-(2H,4H)-dione (DADK), 6-t-butyl-3-(methylthio)-1,2,4-triazin-5(4H)-one (DA) and parent compound, respectively. A substantial portion of the applied radioactivity (56%) was bound to the soil. In the dark control, 4.6, 16.9, 44.0 and 34% of the applied radioactivity was present as DADK, DA, parent or bound compound, respectively.

- Under aerobic conditions, metribuzin at 10 ppm degraded with a half-life of 35-63 days in silt loam and sandy loam soils treated with a 50% wettable powder (WP) formulation, and 63 days in soils treated with a 4-lb/gal FlC formulation (Pither and Gronberg, 1976). Degradates found were: 6-t-butyl-1,2,4-triazin-3,5-(2H,4H)-dione (DADK); 4-amino-6-butyl-1-2,4,-triazin-3,5-(2H,4H)-dione (DK); and 6-t-butyl-3-(methylthio)-1,2,4-triazin-5-(4H)-one (DA).

- ^{14}C-Metribuzin residues degraded slowly in silty clay soil under anaerobic conditions with a half-life of more than 70 days (Khasawinah, 1972). After 10 weeks of incubation, 10, 10.9, 57, and 19% of the applied radioactivity was present as DADK, DA, parent compound or bound to the soil, respectively.

- Metribuzin adsorption was significantly correlated to soil organic matter, clay and bar soil water contents (Savage, 1976). Calculated K_d values ranged from 0.27 for a sandy loam soil (0.75% organic matter, 11% clay and 12% of 0.33 bar soil water content), to 3.41 for a clay soil (42% organic matter, 71% clay and 42% of 0.33 bar soil water content).

- ^{14}C-Metribuzin residues were very mobile in Amarillo sandy loam and Louisiana Commerce silt loam soils; after leaching 12-inch soil columns with 20 inches of water, 96.6 and 91.6% of the applied radioactivity, respectively, was found in the leachate (Houseworth and Tweedy, 1973). ^{14}C-Metribuzin residues were relatively immobile in Indiana silt loam and New York muck soils; after leaching 12-inch soil columns, 90.6 and 89.4% of the applied radioactivity was detected in the top 3 cm of the Indiana silt loam and New York muck, soil columns, respectively. No radioactivity was detected in column leachates.

- ^{14}C-Metribuzin residues (test substance not characterized) aged 30 days were moderately mobile in an Amarillo sandy loam soil column; after leaching a 12-inch column with 22.5 inches of water, 7.3% of the applied radioactivity was found in the leachate (Tweedy and Houseworth, 1974). In the soil column, 85.2% of the applied radioactivity remained within the top 2 inches.

- ^{14}C-Metribuzin residues (test substance not characterized) were intermediately mobile in sandy clay loam and silt loam soils (R_f 0.61 to 0.62) and mobile in sandy, sandy loam, and two silty clay soils (R_f 0.68 to 0.77), based on soil thin-layer chromatography (TLC) tests (Thornton et al., 1976). ^{14}C-Metribuzin residues (test substance not characterized) were intermediately mobile in sand (R_f 0.61), sandy clay loam (R_f 0.64), two silty clay soils (R_f 0.62 and 0.71), silt loam (R_f 0.66) and sandy loam (R_f 0.82) soils, based on soil TLC tests (Obrist and Thorton, 1979). ^{14}C-Metribuzin (purity not specified) at 1.5 ug/spot had low mobility (R_f 0.13 to 0.26) in two muck soils and intermediate mobility (R_f 0.42 to 0.53) in six mineral soils ranging in texture from sand to clay, based on soil TLC plates developed in water (Sharon and Stephenson, 1976).

- In the field, metribuzin dissipates with half-lives of less than 1 month to 6 months. Three metribuzin degradates were detected: 6-t-butyl-1,2,4-triain-3,5-(2H,4H)-dione (DADK); 4-amino-6-t-butyl-1,2,4-triazin-3,5-(2H,4H)-dione (DK); and 6-t-butyl-3-(methylthio)1,2,4-triazin-5-(4H)-one (DA). Soil type and characteristics, chemical formulation or application rates did not discernibly affect the dissipation rate of metribuzin (Stanley and Schumann, 1969; Finlayson, 1972; Rockwell, 1972a; Rockwell, 1972b; Rockwell, 1972c; Rowehl, 1972a; Rowehl, 1972b; Schultz, 1972; Mobay Chemical, 1973; Fisher, 1974; Murphy, 1974; United States Borax and Chemical Corp., 1974; Potts et al., 1975; Analytical Biochemistry Laboratories, 1976; Ballantine, 1976; and Ford, 1979).

III. PHARMACOKINETICS

Absorption

- A study was conducted in four dogs using oral dosing of radiolabeled metribuzin (Khasawinah, et al, 1972) to evaluate absorption, distribution and metabolites. Analysis of blood samples showed a peak level at 4 hours.

Distribution

- No information was found in the available literature on the distribution of metribuzin. Khasawinah et al. (1972) did not provide information on distribution of metribuzin in the dog study.

Metabolism

- No information was found in the available literature on the metabolism of metribuzin. Khasawinah et al. (1972) study in dogs did not elaborate on metabolism in metribuzin.

Excretion

- Khasawinah et al. (1972) reported that 52 to 60% of the administered dose of metribuzin in dogs was excreted in the urine and 30% in the feces.

IV. HEALTH EFFECTS

Humans

No information was found in the available literature on the health effects of metribuzin in humans.

Animals

Short-term Exposure

- Crawford and Anderson (1974) reported the acute oral LD_{50} values following the administration of technical metribuzin to guinea pigs and rats as 245 and 1,090 mg/kg, respectively, for male animals, and 274 and 1,206 mg/kg, respectively, for females.

- Mobay Chemical (1978) reported the acute oral LD_{50} values for a wettable granular formulation of metribuzin to be 2,379 and 2,794 mg/kg for male and female rats, respectively.

- Mobay Chemical (1978) reported the acute dermal LD_{50} for a wettable granular formulation of metribuzin to be >5,000 mg/kg for both male and female rats.

- Mobay Chemical (1978) reported the acute (1-hour) inhalation LC_{50} in rats for a wettable granular formulation to be >20 mg/L.

Dermal/Ocular Effects

- In studies conducted by Mobay Chemical (1978), metribuzin (wettable granular) was determined to be a very slight irritant to rabbit eyes and skin.

Long-term Exposure

- Loser et al. (1969) administered metribuzin to Wistar rats (15/sex/dose) for 3 months in their feed at levels of 0, 50, 150, 500 or 1,500 ppm (about 2.5, 7.5, 25 or 75 mg/kg/day, based on the dietary assumptions of Lehman, 1959). Following treatment, food consumption, growth, body weight, organ weight, clinical chemistry, hematology, urinalysis and histopathology were measured. No significant efects on these parameters were observed in either sex at 50 ppm (2.5 mg/kg/day). Among females, enlarged livers were found in the 150, 500 or 1,500 ppm (7.5, 25 or 75 mg/kg/day) dosage groups ($p < 0.05$), and thyroid glands were also enlarged in the 500 or 1,500 ppm (25 or 75 mg/kg/day) groups ($p < 0.05$ and $p < 0.01$, respectively). In the males, enlarged thyroids were reported among the 500 (25 mg/kg/day) ($p < 0.05$) and 1,500 ppm (75 mg/kg/day) ($p < 0.01$) dosage groups, while an enlarged heart was reported at 1,500 ppm (75 mg/kg/day) ($p < 0.05$). At 1,500 ppm (75 mg/kg/day), lower body weights ($p < 0.01$) were reported in both sexes when compared to untreated controls.

- In studies conducted by Lindberg and Richter (1970), beagle dogs (four/sex/dose) administered oral doses of 50, 150 or 500 ppm (about 1.25, 3.75 or 12.5 mg/kg/day, based on the dietary assumptions of Lehman, 1959) technical metribuzin for 90 days showed no significant differences in body weights, food consumption, behavior, mortality, hematologic findings, urinalysis, gross pathology or histopathology.

- Loser and Mohr (1974) reported that dietary concentrations of 25, 35, 100 or 300 ppm metribuzin did not significantly affect physical appearance, behavior, mortality, hematologic clinical chemistry, urinalysis or histopathology in rats (40/sex/dose) fed technical metribuzin in the diet for 24 months. The body weights of females at the 20 mg/kg/day dose level were usually lower ($p < 0.05$) than those of controls; at the end of the test period, however, no significant differences were noted.

- Hayes et al. (1981) administered technical metribuzin in the diet to albino CD mice (50/sex/dose) at 200, 800 or 3,200 ppm (about 30, 120 or 480 mg/kg/day, based on the dietary assumptions of Lehman, 1959) for 24 months. Following treatment, feed consumption, general behavior, body and organ weights, mortality, hematology and histopathology were analyzed. No adverse effects were observed in these parameters in either sex at 800 ppm (120 mg/kg/day). However, a significant ($p < 0.05$) increase in absolute and relative liver and kidney weights was observed in female mice receiving 3,200 ppm (480 mg/kg/day).

- In studies conducted by Loser and Mirea (1974), four groups of beagle dogs (four/sex/dose) were administered metribuzin in the diet at dose levels of 0, 25, 100 or 1,500 ppm (about 0, 0.625, 2.5 or 37.5 mg/kg/day, based on the dietary assumptions of Lehman, 1959) for 24 months. Following treatment, food consumption, general behavior and appearance, clinical chemistry, hematology, urinalysis, body and organ weights and histopathology were evaluated. No toxicologic effects were reported in animals administered 100 ppm metribuzin (2.5 mg/kg/day) or less for any of the parameters measured. Necrosis of the renal tubular cells, slight iron deposition as well as slight hyperglycemia and temporary hypercholesterolemia were noted in animals administered 1,500 ppm (37.5 mg/kg/day).

Reproductive Effects

- In a 3-generation reproduction study, Loser and Siegmund (1974) administered technical metribuzin in the feed at dose levels of 0, 35, 100 or 300 ppm (about 0, 1.75, 5 or 15 mg/kg/day, based on the dietary assumptions of Lehman, 1959) to FB30 (Elberfeld breed) rats during mating, gestation and lactation. Following treatment, fertility, lactation performance and pup development were evaluated. No treatment-related effects were reported at any dose tested.

Developmental Effects

- Unger and Shellenberger (1981) administered technical metribuzin by gastric intubation to pregnant female rabbits (16 to 17/dose) on days 6 through 18 of gestation at daily doses of 15, 45 or 135 mg/kg/day. Following treatment, there was a statistically significant ($p < 0.05$) decrease in body weight gain in the high-dose does (135 mg/kg). No maternal toxicity was reported in animals administered metribuzin at levels of 45 mg/kg/day or less. No treatment-related effects were reported at any dose level in fetuses based on gross, soft tissue and skeletal examinations.

- Machemer (1972) reported no maternal toxicity, embryotoxicity or teratogenic effects following oral administration (via stomach tube) of technical metribuzin to FB30 rats (21 to 22/dose) on days 6 through 15 of gestation at dose levels of 5, 15, 50 or 100 mg/kg/day.

Mutagenicity

- Metribuzin showed no mutagenic activity in several bacterial assays (Inukai and Iyatomi, 1977; Shirasu et al., 1978) or in dominant lethal tests in mice (Machemer and Lorke, 1974, 1976). The results of microbial point mutation assays (Machemer and Lorke, 1974) did not indicate a mutagenic potential for metribuzin in the test systems utilized. The results of dominant lethal mutations in mice or chromosomal aberrations in hamster spermatogonia at dose levels of 300 mg/kg and 100 mg/kg, respectively, did not indicate any mutagenic effects of metribuzin.

Carcinogenicity

- Hayes et al. (1981) conducted studies in which technical metribuzin was administered in the diet to albino CD-1 mice (50/sex/dose) at 200, 800 or 3,200 ppm (approximately 30, 120 or 380 mg/kg/day) for 24 months. Minimal toxic effects were observed at the high-dose level in the form of increased liver weight and changes in the hematocrit and hemoglobin measurements. Although some increase in the number of tumor-bearing animals was observed in low- and mid-dose animals, significant increases in the incidence of specific tumor types were not observed at any dose level. It was concluded that, under the conditions of the test, there was no increase in the incidence of tumors in mice.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of a One-day HA for metribuzin. It is therefore recommended that the Ten-day HA value for a 10-kg child (4.5 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Unger and Shellenberger (1981) has been selected to serve as the basis for determination of the Ten-day HA for metribuzin. In this study, pregnant rabbits (16 or 17/dose) that were administered technical metrizubin by gastric intubation at dosage levels of 0, 15, 45 or 135 mg/kg/day on days 6 through 18 of gestation showed a statistically significant ($p < 0.05$) decrease in body weight gain at the 135-mg/kg dose. No maternal toxicity was reported at or below the 45-mg/kg dose. No treatment-related effects were reported at any dose level in fetuses based on gross, soft tissue and skeletal examinations. The NOAEL identified in this study was, therefore, 45 mg/kg/day.

Using a NOAEL of 45 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(45 \text{ mg/kg/day}) \ (10 \text{ kg})}{(100) \ (1 \text{ L/day})} = 4.5 \text{ mg/L } (5{,}000 \text{ mg/L})$$

where:

45 mg/kg/day = NOAEL, based on absence of body weight reduction in rabbits exposed to metribuzin via gastric intubation on days 6 through 18 of gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The study by Loser et al. (1969) has been selected to serve as the basis for the Longer-term HA for metribuzin. In this study, rats (15/sex/dose) were fed diets containing metribuzin at doses of 50, 150, 500 or 1,500 ppm (about 2.5, 7.5, 25 or 75 mg/kg/day based on calculations in Lehman, 1959) for 90 days. Thyroid glands were enlarged in males in the 500 or 1,500 ppm (25 or 75 mg/kg/day) dosage groups, while the heart was enlarged at the 1,500 ppm (75 mg/kg/day) dose level. In females, enlarged livers were detected in the 150, 500 or 1,500 ppm (7.5, 25 or 75 mg/kg/day) dosage groups, and the thyroid was enlarged in the 500 or 1,500 ppm (25 or 75 mg/kg/day) dosage groups. Body weights were reduced in both sexes at 1,500 ppm (75 mg/kg/day), compared to untreated controls. The NOAEL identified in this study was, therefore, 50 ppm (2.5 mg/kg/day). Lindberg and Richter (1970) determined a NOAEL of 12.5 mg/kg/day in dogs; however, this study was not chosen, since the NOAEL was higher than the LOAEL of 7.5 mg/kg/day identified by Loser et al. (1969) in the rat.

Using a NOAEL of 2.5 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(2.5\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.25\ \text{mg/L}\ (300\ \text{ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of increased absolute organ weights in rats exposed to metribuzin via the diet for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Using a NOAEL of 2.5 mg/kg/day, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(2.5 \text{ mg/kg/day}) \ (70 \text{ kg})}{(100) \ (2 \text{ L/day})} = 0.875 \text{ mg/L } (900 \text{ ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of increased absolute organ weights in rats exposed to metribuzin via the diet for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Loser and Mirea (1974) has been selected to serve as the basis for the Lifetime HA for metribuzin. In this study, dogs (four/sex/dose) were administered metribuzin in the diet at dose levels of 0, 25, 100 or 1,500 ppm (0, 0.625, 2.5 or 37.5 mg/kg/day) for 24 months. Necrosis of the renal tubular cells was reported as well as slight and temporary changes in certain clinical chemistry parameters (e.g., blood glucose and cholesterol) at the high-dose level. No other toxicologic effects were reported. Based on this information, a NOAEL of 100 ppm (2.5 mg/kg/day) and a LOAEL of 1,500 ppm (37.5 mg/kg/day) were reported. Loser and Mirea (1974) reported a NOAEL of 20 mg/kg/day in rats. This study was not selected because no dose-related toxicologic responses were observed, and the rat may be less sensitive than the dog. Hayes et al. (1981) determined a NOAEL of 120 mg/kg/day in mice; however, this value exceeded the LOAEL (37.5 mg/kg/day) reported by Loser and Mirea (1974).

Using this study, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(2.5 \text{ mg/kg/day})}{(100)} = 0.025 \text{ mg/kg/day}$$

where:

2.5 mg/kg/day = NOAEL, based on absence of organ toxicity and clinical chemistry effects in dogs exposed to metribuzin via the diet for 24 months.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.025 \text{ mg/kg/day}) \ (70 \text{ kg})}{(2 \text{ L/day})} = 0.875 \text{ mg/day } (900 \text{ ug/L})$$

where:

0.025 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.875 \text{ mg/L}) \ (20\%) = 0.175 \text{ mg/L } (200 \text{ ug/L})$$

where:

0.875 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- In a study by Hayes et al. (1981), metribuzin was administered in the feed of mice (50/sex/dose) at dose levels of 200, 800 or 3,200 ppm (30, 120 or 480 mg/kg/day) for 24 months. Following treatment, the incidence of tumor formation was analyzed in a variety of tissues. Neoplasms of various tissues and organs were similar in type, location, time of occurrence and incidence in control and treated animals. It was concluded that under the conditions of the test, there was no increase in the incidence of tumors in mice.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of metribuzin.

- Applying the criteria described in EPA's guidelines for assessment of carcinogen risk (U.S. EPA, 1986), metribuzin may be classified in Group D: not classified. This category is used for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- A Threshold Limit Value-Time-Weighted Average (TLV-TWA) of 5 mg/m^3 was determined, based on animal studies substantiated by repeated inhalation tests, a safety factor of 5, and assuming a total pulmonary absorption (ACGIH, 1984).

VII. ANALYTICAL METHODS

- Analysis of metribuzin is by a gas chromatography (GC) method applicable to the determination of certain organonitrogen pesticides in water samples (U.S. EPA, 1985). This method requires a solvent extraction of approximately 1 L of sample with methylene chloride using a separatory funnel. The methylene chloride extract is dried and exchanged to acetone during concentration to a volume of 10 mL or less. The compounds in the extract are separated by GC and measurement is made with a thermionic bead detector. This method has been validated in a single laboratory, and estimated detection limits have been determined for the analytes, including metribuzin; the estimated detection limit is 0.15 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) adsorption and a conventional treatment scheme will remove metribuzin from water.

- Whittaker (1980) experimentally determined adsorption isotherms for metribuzin on GAC.

- Whittaker (1980) reported the results of GAC columns operating under bench-scale conditions. At a flow rate of 0.8 gpm/sq ft and an empty bed contact time of 6 minutes, metribuzin breakthrough (when effluent concentration equals 10% of influent concentration) occurred after 112 bed volumes (Bv).

- In the same study, Whittaker (1980) reported the results for four metribuzin bi-solute solutions when passed over the same GAC continuous flow column.

- Another study investigated the effectiveness of two different GAC columns in removing metribuzin from contaminated wastewater (Whittaker, et al., 1982). One type of GAC showed breakthrough for metribuzin

(6 mg/L) from an initial concentration of 140 mg/L after 50 gallons of the wastewater had been treated. No pesticide was found in the effluent from the second type of GAC.

- Conventional water treatment, coagulation and sedimentation with alum and an anionic polymer removed more than 50% of the metribuzin present (Whittaker et al., 1980). The optimum alum dosage was 200 mg/L. Also equivalent dosages of ferric chloride were found to be equally effective.

- Treatment technologies for the removal of metribuzin from water are available and have been reported to be effective. However, selection of an individual technology or combination of technologies to attempt metribuzin removal from water must be by a case-by-case technical evaluation, and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

PARAQUAT

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

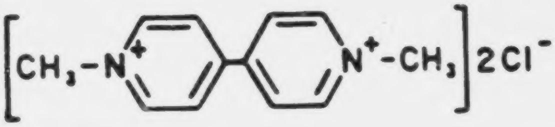
Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

Paraquat, with a chemical name 1,1'-dimethyl-4,4'-dipyridinium ion, is present mostly as the dichloride salt (CAS No. 1910-42-5) or as the dimethyl sulfate salt (CAS No. 2074-50-2, molecular weight 408.48) (Meister, 1988). Contents discussed below pertain to paraquat dichloride.

CAS No. 1910-42-5

Structural Formula



1,1'-Dimethyl-4,4'-bipyridinium-dichloride

Synonyms

- AT-5, Actor, Cekuquat, Crisquat, Herboxone, Dextrone, Dexuron, Esgram, Gramocil, Gramoxone, Gramuron, Goldquat 276, Herbaxon (Agro Quimicas), Herboxone, Mofisal, Osaquat Super, Paracol, Paracote, Pathclear, Preeglone, Priglone, Simpar, Sweep, Terraklene, 'Totacol, Total, Toxer, Weedol. Discontinued name: Ortho (Meister, 1988).

Uses

- Contact herbicide and desiccant used for desiccation of seed crops, for noncrop and industrial weed control in bearing and nonbearing fruit orchards, shade trees, and ornamentals, for defoliation and desiccation of cotton, for harvest aid in soybeans, sugarcane, guar, and sunflowers, for pasture renovation, for use in "no-till" or before planting or crop emergence, dormant alfalfa and clover, directed spray, and for killing potato vines. Paraquat is also effective for eradication of weeds on rubber plantations and coffee plantations and against paddy bund (Meister, 1988).

Properties (ACGIH, 1980; Meister, 1988; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_{12}H_{14}N_2.2Cl$
Molecular Weight	257.18
Physical State	Colorless to yellow crystalline solid
Boiling Point	175 to 180°C
Melting Point	--
Density	1.24 g/mL (20°C)
Vapor Pressure	No measurable vapor pressure
Specific Gravity	1.24 at 20°C/20°C
Water Solubility	Very soluble
Log Octanol/Water Partition Coefficient	2.44 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Paraquat was undetectable in 843 ground water samples analyzed (STORET, 1988). Samples were collected at 813 ground water locations. No surface water samples were collected for analysis.

Environmental Fate

- ^{14}C-Paraquat dichloride (>96.5% pure) at 91 mg/L was stable to hydrolysis at 25 and 40°C at pH 5, 7 and 9 for up to 30 days (Upton et al., 1985).

- Uniformly ring-labeled ^{14}C-paraquat (99.7% pure) at approximately 7.0 ppm in sand did not photodegrade when irradiated with natural sunlight for 24 months (Pack, 1982). No degradation products were detected at any sampling interval. After 24 months of irradiation, >84% of the applied radioactivity was extractable and <4% was unextractable.

- Paraquat was essentially stable to photolysis in soil (Day and Hemingway, 1981). Four degradation products, 1-methyl-4,4'-bipyridylium ion, 4-(1,2-dihydro-1-methyl-2-oxo-4-pyridyl)-1-methyl pyridylium ion, 4-carboxy-1-methyl pyridylium ion, and an unknown, individually constituted <6.0% of the total radioactivity in either irradiated (undisturbed) or dark control soils.

- Paraquat (test substance uncharacterized) at 0.05 to 1.0 ppm in water plus soil declined with a half-life of >2 weeks (Coats et al., 1964). In water only, paraquat declined with a half-life of approximately 23 weeks.

- ^{14}C-Paraquat (test substance uncharacterized) was immobile in silt loam and silty clay loam (R_f 0.00), and slightly mobile in sandy loam (R_f 0.13) soils, based on soil thin-layer chromatography (TLC) tests (Helling and Turner, 1968).

- Methyl-labeled ^{14}C-paraquat (test substance uncharacterized) at 1.0 ppm was stable to volatilization at room temperature over a 64-day period (Coats et al., 1964).

- In a pond treated with paraquat (test substance uncharacterized) at 1.14 ppm (Frank and Comes, 1967), paraquat residues (uncharacterized) declined from 0.55 ppm 1 day after treatment to nondetectable (<0.001 ppm) 18 days after treatment. The dissipation of paraquat residues (uncharacterized) in water was accompanied by a concomitant increase of paraquat residues (uncharacterized) in the soil. Paraquat (test substance uncharacterized) at 0.04 ppm dissipated in pond water with a half-life of approximately 2 days (Coats et al., 1964). For more details, see Calderbank's chapter on paraquat in Herbicides (Calderbank, 1976).

III. PHARMACOKINETICS

Absorption

- In Wistar rats given single oral doses of ^{14}C-paraquat dichloride or dimethyl sulfate by gavage (0.5 to 50 mg/kg, purity not stated), 69 to 96% was excreted unchanged, mostly in feces, and no radioactivity appeared in bile (Daniel and Gage, 1966). Some systemic absorption of the degradation products that were produced in the gut was noted. Approximately 30% of the administered dose appeared in feces in a degraded form.

- ^{14}C-Methyl-labeled paraquat (99.7% purity) was administered orally to a cow in a single dose of approximately 8 mg cation/kg (Leahey et al., 1972). A total of 95.6% of the dose was excreted in feces in the first 3 days. A small amount, 0.7% of the dose, was excreted in the urine, 0.56% during the first 2 days. Only 0.0032% of the dose appeared in the milk.

- A goat was administered ^{14}C-ring-labeled paraquat dichloride (>99% purity) orally at 1.7 mg/kg for 7 consecutive days (Leahey et al., 1976a). At sacrifice, 2.4% and 50.3% of the radioactive dose had been excreted in the urine and feces, respectively, and 33.2% was recovered in the contents of the stomach and intestines. The radioactivity was associated with unchanged paraquat.

- In studies with pigs, ^{14}C-methyl-labeled (Leahey et al., 1976b) and ^{14}C-ring-labeled (Spinks et al., 1976) paraquat (>99% purity) at dose levels of 1.1 and 100 mg ion/kg/day, respectively, was given for up to 7 days. At sacrifice, 69 to 72.5% and 2.8 to 3.4% of the total radioactive dose had been excreted in the feces and urine, respectively.

Distribution

- Pigs were given oral doses of ^{14}C-methyl-labeled (Leahey et al., 1976b) and ^{14}C-ring-labeled (Spinks et al., 1976) paraquat dichloride (>99% purity) for up to 7 consecutive days at dose levels of 1.1 and 100 mg ion/kg/day, respectively. At sacrifice, radioactivity associated mostly with unchanged paraquat was identified in the lungs, heart, liver and kidneys, with trace amounts in the brain, muscle and fat.

- The distribution of radioactivity was studied in a goat fed ^{14}C-ring-labeled paraquat dichloride (1.7 mg/kg/day, 99.7% purity) in the diet for 7 consecutive days (Hendley et al., 1976). Most of the radioactivity was found in the lungs, kidneys and liver. The major residue was unchanged paraquat.

Metabolism

- Paraquat dichloride or paraquat dimethyl sulfate (radiochemical purity: 99.3 to 99.8%), labeled with ^{14}C in either methyl groups or in the ring, was poorly absorbed from the gastrointestinal tract of a cow (Leahey et al., 1972), goats (Hendley et al., 1976), pigs (Leahey et al., 1976b; Spinks et al., 1976) and rats (Daniel and Gage, 1966), and was excreted in the feces mostly as unchanged paraquat. However, after an oral dose, there was microbial degradation of paraquat in the gut. In one study with rats (Daniel and Gage, 1966), 30% of a dose of paraquat appeared in the feces in a degraded form. A portion of these microbial degradation products can be absorbed and excreted in the urine, whereas the remainder is excreted in the feces.

Excretion

- In studies with a cow (Leahey et al., 1972) and rats (Daniel and Gage, 1966), about 96% and 69 to 96%, respectively, of the administered radioactivity (single oral doses, ^{14}C-labeled) from paraquat was excreted in the feces within 2 to 3 days as unchanged paraquat.

- Goats (Hendley et al., 1976) and pigs (Leahey et al., 1976b; Spinks et al., 1976) that received single oral doses of ^{14}C-labeled paraquat (1.7 and 1.1 or 100 mg ion/kg/day, respectively) for up to 7 days excreted 50 and 69%, respectively, of the total administered dose in feces unchanged.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- The Pesticide Incident Monitoring System (U.S. EPA, 1979) indicated numerous cases of poisoning from deliberate or accidental ingestion of paraquat or by dermal and inhalation exposure from spraying, mixing and loading operations. Generally, the concentrations of the ingested doses or of amounts inhaled or spilled on the skin were not specified. Symptoms reported following these exposures included burning of the mouth, throat, eyes and skin. Other effects noted were nausea, pharyngitis, episcleritis and vomiting. No fatalities were reported following dermal or inhalation exposure. Deliberate and accidental ingestion of unspecified concentrations of paraquat resulted in respiratory distress and subsequent death. See also Cooke et al. (1973).

Long-term Exposure

- No information was found in the available literature on long-term human exposure to paraquat.

Animals

Short-term Exposure

- Acute oral LD_{50} values for paraquat (99.9% purity) were reported as 112, 30, 35 and 262 mg paraquat ion/kg in the rat, guinea pig, cat and hen, respectively. (Clark, 1965). Signs of toxicity included respiratory distress and cyanosis among rats and guinea pigs, blood-stained droppings among the hens, and muscular weakness, incoordination and frequent vomiting of frothy secretion among the cats.

- Acute (4-hour) inhalation LC_{50} values for paraquat ranged from 0.6 to 1.4 mg ion/m^3 paraquat (McLean Head et al., 1985).

Dermal/Ocular Effects

- Acute dermal LD_{50} values for rabbits (Standard Oil, 1977) were 59.9 mg/kg and 80 to 90 mg paraquat ion/kg for rats (FDA, 1970).

- Paraquat concentrate 3 (34.4% paraquat ion) was applied (0.5 mL or 172 mg paraquat ion) to intact and abraded skin of six male New Zealand White rabbits for 24 hours (Bullock, 1977b). Very slight, moderate or severe erythema and slight edema were noted during the 7-day observation period for both intact and abraded skin.

- Paraquat concentrate 3 (0.1 mL, 34.4% paraquat ion) was instilled into the conjunctival sac of one eye in each of six male New Zealand White rabbits (Bullock, 1977a). Untreated eyes served as controls. Unwashed eyes were examined for 14 days. Complete opacity of the cornea was reported in three of six rabbits. Roughened corneas, severe pannus, necrosis of the conjunctivae, purulent discharge, severe chemosis of the conjunctivae and mild iritis were also reported.

Long-term Exposure

- Beagle dogs (three/sex/dose) were fed technical o-paraquat (32.2% cation) in the diet for 90 days at dose levels of 0, 7, 20, 60 or 120 ppm (Sheppard, 1981). Assuming that 1 ppm is equivalent to 0.025 mg/kg/day, these levels correspond to doses of 0, 0.18, 0.5, 1.5 or 3 mg paraquat ion/kg/day (Lehman, 1959), respectively. Increased lung weight, alveolitis and alveolar collapse were observed at 60 ppm Lowest-Observed-Adverse-Effect Level (LOAEL), and the No-Observed-Adverse-Effect Level (NOAEL) identified for this study was 20 ppm (0.5 mg paraquat ion/kg/day).

- Alderley Park beagle dogs (six/sex/dose) were fed diets containing technical paraquat (32.3% cation) daily for 52 weeks at dietary levels of 0, 15, 30 or 50 ppm (Kalinowski et al., 1983). Based on actual group mean body weights and food consumption, these values correspond to doses of 0, 0.45, 0.93 and 1.51 mg/kg/day paraquat ion for male dogs and 0, 0.48, 1.00 or 1.58 mg paraquat ion/kg/day for females. Clinical and behavioral abnormalities, food consumption, body weight, hematology, clinical chemistry, urinalysis, organ weights, gross pathology and histopathology were comparable for treated animals and controls at 15 ppm (the lowest dose tested). An increased severity and extent of chronic pneumonitis occurred at 30 ppm (LOAEL) in both sexes, but especially in the males. Based on the results of this study, the NOAEL identified was 15 ppm (0.45 mg paraquat cation/kg/day).

- Technical paraquat dichloride (32.7% cation) was fed to Alderley Park mice (60/sex/dose) for 97-99 weeks at levels of 0, 12.5, 37.5 and 100/125 ppm (100 ppm for the initial 35 weeks and then 125 ppm until termination of the study) (Litchfield et al., 1981). Based on the assumption that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 1.87, 5.6 and 15/18.75 mg cation/kg. The animals were observed for toxic signs, and body weights, food consumption and utilization; urinalysis, gross pathology and histopathology were also evaluated. Renal tubular degeneration in the males, weight loss and decreased food intake in the females, were observed in the 37.5 ppm dose group. Based on these findings, a NOAEL of 12.5 ppm cation (1.87 mg/kg/day) was identified for both sexes.

- Fischer 344 rats (70/sex/dose) were fed diets containing 0, 25, 75 or 150 ppm of technical paraquat (32.7% cation) for 113 to 117 weeks (males) and 122 to 126 weeks (females) (Woolsgrove et al., 1983). Based on the assumption that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 1.25, 3.75 or 7.5 mg cation/kg/day. Clinical signs, food and water consumption, clinical chemistry, urinalysis, hematology, ophthalmoscopic effects, gross pathology and histopathology were evaluated. Increased incidences of slight hydrocephalus were noted in the female rats dying between week 53 and termination of the study; these incidences were 5/60, 8/30, 9/27 and 9/30 rats in the control, low, mid and high dose, respectively. Also, increased incidences of spinal cord cysts and cystic spaces were noted in the male rats dying between week 53 and termination of the study. These incidences were 0/53, 6/36 and 4/35 rats at the control, low and mid-level doses, respectively; no incidence was reported at the high dose. Eye opacities, cataracts and nonneoplastic lung lesions (alveolar macrophages and epithelialization, and slight peribronchiolar lymphoid hyperplasia) were observed at 75 ppm and above. Similar eye lesions occurred at 25 ppm (the lowest dose tested). These effects did not appear to be biologically significant, since they were either minimal or occurred after 104 weeks of treatment. Based on these results, an approximate NOAEL of 25 ppm (1.25 mg cation/kg/day) was identified.

Reproductive Effects

- Lindsay et al. (1982) fed Alderley Park rats technical paraquat dichloride (32.7% cation w/w) in unrestricted diet for three generations at dose levels of 0, 25, 75 or 150 ppm paraquat ion. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 1.25, 3.75 or 7.5 mg/kg/day. No adverse reproductive effects were reported at 150 ppm (the highest dose tested) or less. An increased incidence of alveolar histiocytosis in the lungs of male and female parents (F_0, F_1 and F_2) was observed in the 75- and 150-ppm dose groups. Based on these results, a reproductive NOAEL of >150 ppm (7.5 mg/kg/day, the highest dose tested) and a systemic NOAEL of 25 ppm (1.25 mg/kg/day, the lowest dose tested) were identified.

Developmental Effects

- Young adult Alderley Park mice (number not stated) were administered paraquat dichloride (100% purity) orally by gavage at dose levels of 0, 1, 5 or 10 mg paraquat ion/kg/day on days 6 through 15 of gestation (Hodge et al., 1977). No teratogenic responses were reported at 10 mg ion/kg/day (the highest dose tested) or lower. Partially ossified sternebrae in 26.3% of the fetuses in the high-dose group (10 mg ion/kg/day) and decreased maternal weight gain in the 5-mg ion/kg/day dose group were observed. Based on these results, the developmental NOAEL identified for this study was 5 mg/kg/day, while the maternal NOAEL was 1 mg/kg/day.

- Hodge et al. (1978) dosed Alderley Park rats (29 or 30/dose) by gavage with paraquat dichloride (100% purity) on days 6 through 15 of gestation at dose levels of 0, 1, 5 and 10 mg paraquat ion/kg/day. No teratogenic effects were reported at 10 mg ion/kg/day (the highest dose tested). Maternal body weight gain was significantly decreased ($p \leq 0.001$) at 5 mg ion/kg/day and above. Fetal body weight gain was significantly ($p = 0.05$) decreased at the mid-dose (5 mg/kg/day, LOAEL) and above. Based on these findings, the developmental and maternal NOAEL of 1 mg paraquat ion/kg/day was identified.

Mutagenicity

- Analytical-grade paraquat dichloride (99.6% purity) was weakly mutagenic in human lymphocytes, with and without metabolic activation, at cytotoxic concentrations (1,250 to 3,500 ug paraquat dichloride/mL blood) (Sheldon et al., 1985).

- Technical-grade, 45.7% active ingredient (a.i.) and analytical-grade (99.6% a.i.) paraquat dichloride were weakly positive in the L5178Y mouse lymphoma assay with and without metabolic activation in studies by Clay and Thomas (1985) and Cross (1985), respectively. Statistically significant increases in mutant colonies were observed only at doses below 29% cell survival (Cross, 1985).

- Analytical-grade paraquat dichloride (99.4% a.i.) increased sister-chromatid exchanges (SCE) at nontoxic doses ($\leq$124 ug/mL in non-activated cultures and $\leq$245 ug/mL in S9-supplemented cultures. The induction of increased SCE was more marked in the absence of the S9 fraction (Howard et al., 1985).

- Mutagenic activity was detected in various assays with *Salmonella typhimurium* (Benigni et al., 1979), human embryo epithelial cells (Benigni et al., 1979) and *Saccharomyces cerevisiae* (Parry, 1977).

Carcinogenicity

- Technical paraquat dichloride (32.7% paraquat ion) fed to Alderley Park mice (60/sex/dose) for 99 weeks did not induce statistically significant dose-related oncogenic responses at dose levels of 0, 12.5, 37.5 or 100/125 ppm (100 ppm for the initial 35 weeks and then

125 ppm until termination of the study) (Litchfield et al., 1981). Based on the assumption that ' ppm in food in mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 1.87, 5.6 and 15/18.75 mg/kg. The study appeared to have been conducted properly. The results show that paraquat is not oncogenic at the dose levels tested.

° Woolsgrove et al. (1983) fed Fischer 344 rats (70/sex/dose) diets containing technical paraquat (32.69%) for 113 to 117 weeks (males) and 122 to 124 weeks (females) at dietary levels of 0, 25, 75 and 150 ppm. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 1.25, 3.75 and 7.5 mg paraquat cation/kg/day. The predominant tumor types noted in this study were tumors of the lungs, endocrine glands (pituitary, thyroid and adrenal) and of the skin and subcutis. Both the lung and endocrine tumors occurred at a frequency similar to the incidence of these kinds of tumors in the historical control. Only when pooled, the skin tumors (squamous cell carcinomas in the head region including ear, nasal cavity, oral cavity and skin) appeared to provide some equivocal evidence of carcinogenicity in the high-dose males. However, the observed skin tumors were low in incidence and occurred at different sites in the head region. The different tumor sites were considered to be anatomically different and inappropriate for pooling by an independent pathology evaluation review (Experimental Pathology Laboratory, Inc.) as well as by the second EPA Review of Paraquat (1988). Thus, the tumors could not be associated with oral exposure to the compound.

° Paraquat dichloride (98% pure) fed to JCR:ICR mice (60/sex/group) at 0, 2, 10, 30 or 100 ppm for 104 weeks did not induce statistically significant dose-related oncogenic responses (Toyoshima et al., 1982a). At 100 ppm, increased mortality and statistically significant changes in hematology, clinical chemistry and organ weights were observed in both sexes, indicating an MTD was reached. The experiment identifies a NOAEL of 30 ppm.

° Paraquat dichloride (98% pure) fed to JCR:Wistar rats (50/sex/group) at 0, 6, 30, 100 or 300 ppm in the diet for 104 weeks did not cause compound-related neoplastic changes (Toyashima et al., 1982b). At 300 ppm, increased mortality, and statistically significant changes in hematology, clinical chemistry and organ weights were observed for males and females, indicating an MTD was reached. The experiment identifies a NOAEL of 100 ppm.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

____ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable information was found in the available literature for the determination of the One-day HA value for paraquat. It is therefore recommended that the Ten-day HA value for the 10-kg child of 0.1 mg/L (100 ug/L), calculated below, be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The rat developmental study (Hodge et al., 1978) has been selected to serve as the basis for the determination of the Ten-day HA value for paraquat. In this study, Alderley Park rats were administered paraquat (100% purity) during gestation days 6 through 15 at dose levels of 0, 1, 5 or 10 mg paraquat ion/kg/day. There was a statistically significant ($p \leq 0.001$; $p = 0.05$) decrease in maternal and fetal body weight gain at the 5-mg paraquat ion/kg/day dose; also at 5 mg/kg/day, there was a slight retardation in ossification. The fetotoxic and maternal NOAEL identified in this study was 1 mg paraquat ion/kg/day. Another adequate study of comparable duration reported a NOAEL of 5 mg/kg/day for developmental effects, and a NOAEL of 1 mg/kg/day for maternal effects supports this selection (Hodge et al., 1977).

Using a NOAEL of 1 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(1 \text{ mg/kg bw/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.1 \text{ mg/L } (100 \text{ ug/L})$$

where:

1 mg/kg/day = NOAEL, based on the absence of fetotoxic and maternal effects in rats exposed to paraquat by gavage on days 6 through 15 of gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

No subchronic studies were found in the available literature that were suitable for deriving the Longer-term HA value for paraquat. The 90-day oral study of dogs (Sheppard, 1981) reported a NOAEL (0.5 mg ion/kg/day) which is similar to the NOAEL (0.45 mg ion/kg/day) of the 52-week oral dog study (Kalinowski et al., 1983) used to derive the Lifetime HA. It is, therefore, recommended that the Drinking Water Equivalent Level (DWEL) of 0.2 mg/L (200 ug/L), calculated below, be used for the Longer-term HA value for an adult, and that the DWEL adjusted for a 10-kg child, 0.05 mg/L (50 ug/L), be used for the Longer-term HA value for a child.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Kalinowski et al. (1983) has been selected to serve as the basis for the Lifetime HA value for paraquat. In this 52-week feeding study in beagle dogs, a NOAEL of 15 ppm (0.45 mg paraquat ion/kg/day) was identified based on the absence of hematological, biochemical, gross pathological and histological effects as well as the absence of any significant changes in food consumption, or in body and organ weights for treated and control groups. Adequate studies of comparable duration reported NOAELs higher than those of the critical study selected for derivation of the Lifetime HA. A lifetime oral study in rats (Woolsgrove et al., 1983) reported a NOAEL of 25 ppm (about 1.25 mg/kg/day); a NOAEL of 12.5 ppm (about 1.87 mg/kg/day) was identified for mice (Litchfield et al., 1981).

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.45 \text{ mg ion/kg/day})}{(100)} = 0.0045 \text{ mg/kg/day}$$

where:

0.45 mg ion/kg/day = NOAEL, based on the absence of biochemical, hematological, gross pathological and histopathological effects in dogs fed paraquat in the diet for 52 weeks.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.0045\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.16\ \text{mg/L}\ (200\ \text{ug/L})$$

where:

0.0045 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Calculation of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.16\ \text{mg/L})\ (20\%) = 0.03\ \text{mg/L}\ (30\ \text{ug/L})$$

where:

0.16 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Based on the recent EPA Peer Review of the data on paraquat (U.S. EPA, 1988a), the chemical is classified in Group E, evidence of noncarcinogenicity for humans (U.S. EPA, 1986). The chemical provided, at most, only equivocal evidence for skin tumors at high dose in male rats (but not in the females) in one study, but no evidence for carcinogenicity in three other studies in rats and mice. The observed skin tumors were low in incidence, occurred at different sites in the head region, and the tumor incidence was significantly different from controls only when pooled from all sites in the head region. Since pooling of the different tumor sites was considered by pathologists to be inappropriate, the tumors could not be associated with oral exposure to the compound.
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of paraquat.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

° The Office of Pesticide Programs (OPP) has established tolerances on raw agricultural commodities for paraquat ion derived from either the bis(methyl sulfate) or dichloride salt ranging from 0.01 to 5 ppm (U.S. EPA, 1984). The tolerances are based on an ADI of 0.0045 mg/kg/day derived from a 1-year feeding study in dogs, with a NOAEL of 0.45 mg/kg/day and a safety factor of 100.

° The National Academy of Sciences (NAS, 1977) has a Suggested-No-Adverse-Response-Level (SNARL) of 0.06 mg/L. This was calculated using an uncertainty factor of 1,000 and a NOAEL of 8.5 mg/kg/day identified in the 2-year rat study by Chevron Chemical Company (1975), with an assumed consumption of 2 L/day of water by a 70-kg adult, with the assumption that 20% of total intake of paraquat was from water.

° The American Conference of Governmental Hygienists has presented a threshold limit value of 0.1 mg/m^3 for paraquat of respirable particle sizes (ACGIH, 1980).

VII. ANALYTICAL METHODS

° Paraquat is analyzed by a Draft EPA method (U.S. EPA, 1988b) for drinking water. In this procedure a measured quantity of sample is extracted with a solid phase adsorbant. After elution from the adsorbant tube, the paraquat residue is determined by high performance liquid chromatography with an ultraviolet detector (HPLC/UV). The method has a single laboratory validation maximum detection limit (MDL). For paraquat, the MDL is 0.80 ug/L.

VIII. TREATMENT TECHNOLOGIES

° Weber et al. (1986) investigated the adsorption of paraquat and other compounds by charcoal and cation and anion exchange resins and their desorption with water. They developed Freundlich adsorption-desorption isotherms for paraquat on charcoal. When 250 mg of charcoal was added to paraquat solutions, it exhibited the following adsorptive capacities: 37.3 and 93.2 mg paraquat/g charcoal at concentrations of 0.373 mg/L and 37.3 mg/L, respectively. Paraquat was also adsorbed by IR-120 exchange resins (H^+ and Na^+ forms). The IR-120-H resin showed more affinity towards paraquat than the IR-120-Na resin. When 665 mg of paraquat in solution was added to 15 mg of resin, IR-120-H adsorbed 70% of paraquat while the IR-120-Na adsorbed 66% of paraquat.

° MacCarthy and Djebbar (1986) evaluated the use of chemically modified peat for removing paraquat from aqueous solutions under a variety of experimental conditions. Paraquat sorption isotherms on treated Irish peat were determined by equilibrating 100-mL volumes of 3.66 mg/L paraquat with 0.1 g of peat at ambient conditions. Tests indicated that equilibrium for paraquat was achieved after 6 days. Peat exhibited the following paraquat sorption capacities: 40, 55 and 60 mg paraquat/g peat at concentrations of 2, 4 and 6 mg/L, respectively. The effects of pH, ionic strength and flow rate on paraquat removal efficiency were also investigated. When 45 mL of 16-mg/L paraquat solution was gravity fed to a column with a diameter of 6 mm that had been packed with 700 mg treated peat, 95 to 99% paraquat removal efficiency was reported without a significant effect by variations in pH, ionic strength or flow rate.

° In summary, several techniques for the removal of paraquat from water have been examined. While data are not unequivocal, it appears that adsorption of paraquat by charcoal, ion exchange and modified peat are effective treatment techniques. However, selection of individual or combinations of technologies for paraquat removal from water must be based on a case-by-case technical evaluation and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

PICLORAM

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

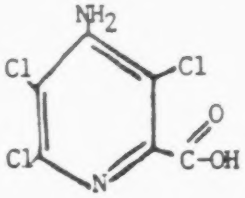
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1918-02-01

Structural Formula



(4-amino-3,5,6-trichloropicolinic acid)

Synonyms

- Amdon; ACTP; Borolin; K-PIN; Tordon (Meister, 1987).

Uses

- Broad-spectrum herbicide for the control of broadleaf and woody plants in rangelands, pastures and rights-of-way for powerlines and highways (Meister, 1987).

Properties (Meister, 1987)

Chemical Formula	$C_6H_3Cl_3N_2O_2$
Molecular Weight	241.6
Physical State (Room Temp.)	White powder
Boiling Point	Decomposes
Melting Point	215°C (decomposes)
Density	--
Vapor Pressure (35°C)	6.2×10^{-7} mm Hg
Specific Gravity	--
Water Solubility	0.043 g/100 mL (free acid) 40 g/100 mL (salts)
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	(Chlorine-like)
Conversion Factor	--

Occurrence

- Picloram has been found in 420 of 744 surface water samples analyzed and in 3 of 64 ground water samples (STORET, 1988). Samples were collected at 135 surface water locations and 30 ground water locations, and picloram was found in 7 states. The 85th percentile of all nonzero samples was 0.13 ug/L in surface water and 0.02 ug/L in ground water sources. The maximum concentration found was 4.6 ug/L in surface water and 0.02 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- The main processes for dissipation of picloram in the environment are photodegradation and aerobic soil degradation. Field tests conducted in Texas with a liquid formulation of picloram have indicated that approximately 74% of the picloram originally contained in the test ecosystems, which included the soil, water and vegetation, was dissipated within 28 days after application (Scifres et al., 1977).

- Photodegradation of picloram occurs rapidly in water (Hamaker, 1964; Redemann, 1966; Youngson, 1968; Youngson and Goring, 1967), but is somewhat slower on a soil surface (Bovey et al., 1970; Merkle et al., 1967; Youngson and Goring, 1967). Hydrolysis of picloram is very slow (Hamaker, 1976).

- Laboratory studies have shown that under aerobic soil conditions, the half-life of picloram is dependent upon the applied concentration, and the temperature and moisture of the soil. The major degradation product is CO_2; other metabolites are present in insignificant amounts (McCall and Jefferies, 1978; Merkle et al., 1967; Meikle et al., 1970, 1974; Meikle, 1973; Hamaker, 1975). In the absence of light under anaerobic soil and aquatic conditions, picloram degradation is extremely slow (McCall and Jefferies, 1978).

- Following normal agricultural, forestry and industrial applications of picloram, long-term accumulation of picloram in the soil generally does not occur. In the field, the dissipation of picloram will occur at a faster rate in hot, wet areas compared to cool, dry locations (Hamaker et al., 1967). The half-life of picloram under most field conditions is a few months (Youngson, 1966). There is little potential for picloram to move off treated areas in runoff water (Fryer et al., 1979). Although picloram is considered to have moderate mobility (Helling, 1971a,b), leaching is generally limited to the upper portions of most soil profiles (Grover, 1977). Instances of picloram entering the ground water are largely limited to cases involving misapplications or unusual soil conditions (Frank et al., 1979).

III. PHARMACOKINETICS

Absorption

- Picloram is readily absorbed from the gastrointestinal (GI) tract of rats (Nolan et al., 1980). Within 48 hours after dosing rats with 1400 mg/kg body weight (bw), 80 to 84% of the dose was found in urine.

- A 500-kg Holstein cow was administered 5 ppm picloram in the feed for 4 days (approximately 0.23 mg/kg/day). Ninety-eight percent of the total dose was excreted in the urine, demonstrating nearly complete absorption (Fisher et al., 1965).

- Similar results were observed in three male Fischer CDF rats receiving ^{14}C-picloram (dose not specified), where 95% of the dose was absorbed (Dow, 1983).

Distribution

- Picloram appears to be distributed throughout the body, with the highest concentration in the kidneys (Redemann, 1964). In rats (strain, age and sex not specified) administered a single 20 mg/kg dose of ^{14}C-labeled picloram in food, radioactivity was found in abdominal fat, liver, muscle and kidneys with maximum levels occurring 2 to 3 hours after dosing.

- Hereford-Holstein steers fed picloram at daily doses of 3.2 to 23 mg/kg for 2 weeks had tissue concentrations of 0.05 to 0.32 mg/kg in muscle, 0.06 to 0.45 mg/kg in fat, 0.12 to 1.6 mg/kg in liver, 0.18 to 2.0 mg/kg in blood and 2 to 18 mg/kg in kidney (Kutschinski and Riley, 1969).

- In a similar study, two steers (strain not specified) fed 100 or 200 mg picloram (3 or 6 mg/kg bw/day) for 31 days had picloram concentrations of 4 or 10 mg/kg, respectively, in the kidneys, while concentrations in other tissues (muscle, omentum fat, heart, liver, brain) were less than 0.5 mg/kg (Leasure and Getzander, 1964).

Metabolism

- Picloram administered to rats or cattle was excreted in the urine in unaltered form (Fisher et al., 1965; Nolan et al., 1980; Dow, 1983), and no $^{14}CO_2$ was detected in expired air of rats given ^{14}C-carbon-labeled picloram (Redemann, 1964; Nolan et al., 1980; Dow, 1983). These studies indicate that picloram is not metabolized significantly by mammals.

Excretion

- Picloram administered to rats is excreted primarily in the urine (Redemann, 1964; Nolan et al., 1980; Fisher et al., 1965).

- Male (F344) rats that were administered a single oral dose of picloram at 1,400 mg/kg bw, within 48 hours excreted 80 to 84% of the dose in the urine, 15% in the feces, less than 0.5% in the bile and virtually no measurable amount as expired CO_2 (Nolan et al., 1980).

- One Holstein cow administered 5 ppm picloram (approximately 0.23 mg/kg/day) in feed for 4 consecutive days excreted more than 98% of the dose in the urine (Fisher et al., 1965).

- In male F344 rats administered picloram at 10 mg/kg bw orally, clearance of picloram from the plasma was biphasic, showing half-lives of 29 and 228 minutes. When administered the same dose intravenously, biphasic clearance occurred with half-lives of 6.3 and 128 minutes (Nolan et al., 1980).

- Cattle excrete picloram primarily in the urine (Fisher et al., 1965), although small amounts may appear in the milk (Kutschinski and Riley, 1969). In Holstein cows fed picloram for 6 to 14 days at doses of 2.7 mg/kg/day or less, no picloram could be found in the milk, while cows fed picloram at doses of 5.4 to 18 mg/kg/day had milk levels up to 0.28 mg/L. This corresponds to 0.02% of the ingested dose. When picloram feeding was discontinued, picloram levels in milk became undetectable within 48 hours.

- Nolan et al. (1983) investigated the excretion of picloram in humans. Six male volunteers (40- to 51-years old) ingested picloram at 0.5 or 5 mg/kg in approximately 100 mL of grape juice. Seventy-six percent of the dose was excreted unchanged in the urine within 6 hours (half-life of 2.9 hours). The remainder was eliminated with an average half-life of 27 hours. The authors did not report observations, if any, of adverse effects. Thus, excretion of picloram in humans was biphasic, as had been demonstrated in rats by Nolan et al. (1980).

IV. HEALTH EFFECTS

Humans

- No information on the health effects of picloram in humans was found in the available literature. In the excretion study by Nolan et al. (1983), described above, the authors did not address the presence of toxic effects in human volunteers ingesting picloram at 0.5 or 5 mg/kg.

Animals

Short-term Exposure

- The acute oral toxicity of picloram is low. Lethal doses have been estimated in a number of species, with LD_{50} values ranging from 2,000 to 4,000 mg/kg (NIOSH, 1980; Dow 1983).

- In a 7-day feeding study by Dow (1981a), picloram was fed to female dogs (one/dose) at dose levels of 400, 800 or 1,600 mg/kg bw/day. Picloram was acutely toxic (emesis, loss of body weight) to female dogs at the higher doses and not toxic at 400 mg/kg/day (the lowest dose tested), which was identified as the NOAEL.

- In a 7- to 14-day study by Dow (1981b), beagle dogs (one dog per dose) were administered picloram (79.4% Tordon) at dose levels of 0, 250, 500 or 1000 mg/kg/day. Based on 79.4% active ingredient, actual doses administered were 200, 400 or 800 mg/kg/day. The No-Observed-Adverse-Effect Level (NOAEL) was determined to be 200 mg/kg/day, the lowest dose tested, based on the absence of reduced food intake.

- In a 32-day feeding study by Dow (1980), picloram was administered to mice at dose levels of 0, 90, 270, 580, 900 or 2,700 mg/kg/day. The NOAEL was 900 mg/kg/day, and the Lowest-Observed-Adverse-Effect Level (LOAEL) was 2700 mg/kg/day, based on increased liver weight.

Dermal/Ocular Effects

- Most formulations of picloram have been evaluated for the potential to produce skin sensitization reactions in humans. Dow (1983) reported in summary data that Tordon 22K was not a sensitizer following an application as a 5% solution. A formulation of Tordon 101 containing 6% picloram acid and 2,4-D acid was not a sensitizer as a 5% aqueous solution in humans (Gabriel and Gross, 1964). When the triisopropanolamine salts of picloram and 2,4-D (Tordon 101) were applied as a 5% solution, sensitization occurred in several individuals; however, when applied alone, the individual components were nonreactive.

Long-term Exposure

- Subchronic studies with picloram have been conducted by Dow (1983), using three species (dogs, rats, mice) over periods of 3 to 6 months. A 6-month study was conducted with beagle dogs that received picloram at daily doses of 0, 7, 35 or 175 mg/kg/day (six/sex/dose group) (Dow, 1983). Increased liver weights were observed at the highest dose (175 mg/kg/day) for males and females, and at the intermediate dose (35 mg/kg/day) for males. Therefore, the 7-mg/kg/day dose level was considered to be a NOAEL.

- In a 13-week feeding study, CDF Fischer 344 rats (15/sex/dosage group) were fed picloram in their diet at dose levels of 0, 15, 50, 150, 300 or 500 mg/kg/day (Dow, 1983). Liver swelling was observed in both sexes at the 150- and 300-mg/kg/day dose levels. The NOAEL in this study was identified as 50 mg/kg/day.

- Ten male and female B6C3F$_1$ mice were administered picloram in their diet at dose levels of 0, 1,000, 1,400 or 2,000 mg/kg/day for 13 weeks (Dow, 1983). Liver weights were increased significantly (p values not reported) in females and males at all dose levels tested.

- Picloram (94%) was fed to Fischer 344 rats (50/sex/dose) for two years in the diet at dose levels of 0, 20, 60 or 200 mg/kg (Dow, 1986). There was a significant dose-related increase in size and altered tictorial properties of centrolobular hepatocytes and increased relative liver weights in males and females dosed at 60 and 200 mg/kg/day. The LOAEL based on histologic changes in the liver is 60 mg/kg/day and the NOAEL is 20 mg/kg/day.

- Osborne-Mendel rats receiving picloram at 370 or 740 mg/kg/day in the diet for 2 years had renal disease resembling that of the natural aging process (NCI, 1978). Increased indices of parathyroid hyperplasia, polyarteritis, testicular atrophy and thyroid hyperplasia and adenoma were observed. Polyarteritis may be indicative of an autoimmune effect.

Reproductive Effects

- As described above in the 2-year feeding study by NCI (1978), testicular atrophy was observed in male Osborne-Mendel rats receiving picloram at 370 or 740 mg/kg/day.

- Groups of 4 male and 12 female rats were maintained on diets containing 0, 7.5, 25 or 75 mg/kg/day of Tordon (95% picloram) through a three-generation (two litters per generation) fertility, reproduction, lactation and teratology study (McCollister et al., 1967). The rats were 11-weeks old at the start of the study and were maintained on the test diets for 1 month prior to breeding to produce the F_{1a} generation. Records were kept of numbers of pups born live, born dead or killed by the dam; litter size was culled to eight pups after 5 days. Lactation continued until the pups were 21-days old, when they were weaned and weighed. After a 7- to 10-day rest, the dam was returned for breeding the F_{1b} generation. The second generation (F_{2a} and F_{3b}) was derived from F_{2b} animals after 110 days of age. Two weanlings per sex per dose from litters of each generation were observed for gross pathology. Gross pathology was also assessed on all parent rats and all females not becoming pregnant. Five male and five female weanlings from each group of the F_{3b} litter were selected randomly for gross and microscopic examination (lung, heart, liver, kidney, adrenals, pancreas, spleen and gonads). Picloram reduced fertility in the F_{1b} generation which was fed 75 mg/kg/day dose. No other effects were noted. Based on these results, a NOAEL of 25 mg/kg/day was identified.

Developmental Effects

- In the McCollister et al. (1967) study described above, the F_{1c}, F_{2c} and F_{3c} litters were used to study the teratogenic potential of picloram. The dams were sacrificed on day 19 or 20 of gestation, and offspring were inspected for gross abnormalities, including skeletal and internal structures, and placentas were examined for fetal death or resorptions. None were observed at any dose level.

- Thompson et al. (1972) administered picloram in corn oil to pregnant Sprague-Dawley rats on days 6 to 15 of gestation. Four groups of 35 rats (25 for the teratology portion and 10 for the postnatal portion of the study) received picloram at 0, 500, 750 or 1,000 mg/kg/day by gavage. Rats were observed daily for signs of toxicity. Prebreeding and gestation day 20 body weights were obtained on teratology rats and prebreeding and postpartum day 21 body weights were obtained for signs of maternal toxicity, while rats given 750 or 1,000 mg/kg/day developed hyperesthesia and mild diarrhea after 1 to 4 days of treatment; 14 maternal deaths occurred between days 8 and 17 of gestation in these dose groups. Evidence of retarded fetal development as reflected by an increase in unossified fifth sternebrae, was observed in all treatment groups but did not occur in a dose-related manner; The occurrence of bilateral accessory ribs was increased significantly in fetuses of dams given 1,000 mg/kg for 10 days during gestation.

At this dose level, there was also maternal toxicity . Since adverse effects occurred at all doses, the LOAEL was 500 mg/kg, the lowest dose tested.

Mutagenicity

- The mutagenic activity of picloram has been studied in a number of microbial systems. Ames tests in several Salmonella typhimurium strains indicated that picloram was not mutagenic with or without activation by liver microsomal fractions (Andersen et al., 1972; Torracca et al., 1976; Carere et al., 1978).

- One study using the same system as above found picloram to be weakly mutagenic (Ercegovich and Rashid, 1977).

- Picloram was shown to be negative in the reversion of bacteriophage AP72 to T_4 phenotype (Andersen et al., 1972), but positive in the forward mutation spot test utilizing Streptomyces coelicolor (Carere et al., 1978).

- Irrespective of a weak mutagenic response in the Salmonella typhimurium test (Ercegovich and Rashid, 1977) and a positive forward mutation, the authors take the position that picloram is not mutagenic. In addition, studies in male and female Sprague-Dawley rats fed picloram at dose levels of 20, 200 or 2,000 mg/kg/day in which no cytological changes in bone marrow cells were observed (Mensik et al., 1976).

Carcinogenicity

- Picloram (at least 90% pure) was administered by diet to Osborne-Mendel rats and B6C3F$_1$ mice (NCI, 1978; also reviewed by Reuber, 1981). Pooled controls from carcinogenicity studies run in the same laboratory (and room, at the Gulf South Research Institute) and overlapping this study by at least 1 year were used. Fifty male rats were dosed with picloram at 208 or 417 mg/kg/day and 50 female rats were dosed at 361 or 723 mg/kg/day. During the second year, rough hair coats, diarrhea, pale mucous membranes, alopecia and abdominal distention were observed in treated rats. In addition, a relatively high incidence of follicular hyperplasia, C-cell hyperplasia and C-cell adenoma of the thyroid occurred in both sexes. However, the statistical tests for adenoma did not show sufficient evidence for association of the tumor with picloram administration. An increased incidence of hepatic neoplastic nodules (considered to be benign tumors) was observed in treated animals. In male rats, the lesion appeared in only three animals of the low-dose treatment group and was not significant when compared to controls. However, the trend was significantly dose-related in females ($p = 0.016$). The incidence in the high-dose group was significant ($p = 0.014$) when compared with that of the pooled control group. The incidences of foci of cellular alteration of the liver were: female rats - matched controls 0/10, low-dose 8/50, high-dose 18/49; male rats - matched controls 0/10, low-dose 12/49, high-dose 5/49. Thus, there is evidence that picloram induced benign neoplastic nodules in the livers of rats of both sexes, but especially those of the females. Subsequent laboratory review by the National Toxicology Program (NTP) has questioned the findings of this study because animals with exposure to known carcinogens were placed in the same room with these animals and cross-contamination might have occurred.

- In the same study, NCI (1978), 50 male and 50 female mice received picloram at 208 or 417, and 361 or 723 mg/kg/day, respectively. Body weights of mice were unaffected, and no consistent clinical signs attributable to treatment were reported during the first 6 months of the study, except isolated incidences of tremors and hyperactivity. Later, particularly in the second year, rough hair coats, diarrhea, pale mucous membranes, alopecia and abdominal distention occurred. No tumors were found in male or female mice or male rats at incidences that could be significantly related to treatment. It was concluded that picloram was not a carcinogen for $B6C3F_1$ mice.
- Dow (1986) retested picloram (94% pure) in a 2-year chronic feeding/oncogenicity study in Fisher 344 rats. Rats (50/sex/dose) were fed 0, 20, 60 or 200 mg/kg/day. Oncogenic effects above those of controls were absent in this study.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for picloram. It is, therefore, recommended that the Ten-day HA value for a 10-kg child (20 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The 7- to 14-day study in dogs by Dow (1981b) has been selected to serve as the basis for the Ten-day HA value for picloram because dogs appear to be the most sensitive species. Doses of 200, 400 or 800 mg/kg/day were used and the dose of 200 mg/kg/day was identified as the NOAEL for short-term exposures based on reduced food intake. Other short-term studies include a 7-day study in dogs by Dow (1981a) with a NOAEL of 400 mg/kg/day and a 32-day study in mice by Dow (1980) with a NOAEL of 900 mg/kg/day.

Using a NOAEL of 200 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(200\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 20\ \text{mg/L}\ (20{,}000\ \text{ug/l})$$

where:

200 mg/kg/day = NOAEL based on the absence of reduced feed intake in beagle dogs exposed to picloram for 7 to 14 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The study by Dow (1983) has been selected to serve as the basis for the Longer-term HA value for picloram because dogs have been shown to be the species most sensitive to picloram. In this study, picloram was fed for 6 months to beagle dogs (six/sex/group) in the diet at dose levels of 0, 7, 35 or 175 mg/kg/day. At 175 mg/kg/day, the following adverse effects were observed in both male and female dogs: decreased body weight gain, food consumption and alanine transaminase levels, increased alkaline phosphatase levels, absolute liver weight and relative liver weight. At 35 mg/kg/day, increased absolute and relative liver weights were noted in males. No compound-related effects were detected in females at 35 mg/kg/day or in males or females at 7 mg/kg/day. Based on these data, 7 mg/kg/day was identified as the NOAEL for dogs for a 6-month exposure.

Using this study, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(7\ \text{mg/kg/day})\ (10)}{(100)\ (1\ \text{L/day})} = 0.7\ \text{mg/L}\ (700\ \text{ug/L})$$

where:

7 mg/kg/day = NOAEL, based on the absence of relative and absolute liver weight changes.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(7 \text{ mg/kg/day})\ (70)}{(100)\ (2 \text{ L/day})} = 2.45 \text{ mg/L } (2{,}000 \text{ ug/L})$$

where:

7 mg/kg/day = NOAEL, based on the absence of relative and absolute liver weight changes.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Dow (1983), chosen for the Longer-term Health Advisory has also been chosen to calculate the Lifetime HA value for picloram. In this study, picloram was fed for 6 months to beagle dogs (six/sex/group) in the diet at dose levels of 0, 7, 35 or 175 mg/kg/day. At 175 mg/kg/day, the following adverse effects were observed in both male and female dogs: decreased body alkaline phosphatase levels, absolute liver weight and relative liver weight. At 35 mg/kg/day, increased absolute and relative liver weights were noted in males. No compound-related effects were detected in females at 35 mg/kg/day or in males or females at 7 mg/kg/day. Based on these data, 7 mg/kg/day was identified as the NOAEL for dogs for a 6-month exposure. The results of this study were chosen, even though they reflect less than lifetime exposure, because the results indicate that the dog is more sensitive than the rat in a long term exposure. Therefore, the Lifetime HA for picloram is determined as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(7\ \text{mg/kg/day})}{(100)} = 0.07\ \text{mg/kg/day}$$

where:

7 mg/kg/day = NOAEL, based on the absence of relative and absolute liver weight changes.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.07\ \text{mg/kg/day})\ (70)}{(2\ \text{L/day})} = 2.45\ \text{mg/L}\ (2{,}000\ \text{ug/L})$$

where:

0.07 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (2.45\ \text{mg/L})\ (20\%) = 0.49\ \text{mg/L}\ (500\ \text{ug/L})$$

where:

2.45 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

° The National Cancer Institute conducted studies on the carcinogenic potential of picloram in rats and mice (NCI, 1978; this study was also reviewed by Reuber, 1981). In the study with mice, there was no indication of an oncogenic response from dietary exposure which included levels of more than 5,000 ppm picloram (723 mg/kg/day) for the greater part of their lifetime. The rat study, however, was negative for oncogenic effects in males, while female rats exhibited a statistically significant increase in neoplastic nodules in the liver. On a time-weighted average, exposures ranged up to 14,875 ppm (743 mg/kg/day) picloram in the diet. Results of the rat study are questionable since possible cross-contamination may have occurred.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of picloram.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), picloram may be classified in Group D: not classified. This group is generally used for substances with inadequate human and animal evidence of carcinogenicity or for which no data are available.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA Office of Pesticide Programs has set an RfD for picloram at 0.07 mg/kg/day (U.S. EPA, 1986b).
- Tolerances have been established for picloram in or on raw agricultural commodities (U.S. EPA, 1986c).
- The National Academy of Sciences (NAS, 1983) has calculated a chronic Suggested-No-Adverse-Response-Level (SNARL) of 1.05 mg/L for picloram. An uncertainty factor of 1,000 was used because the issue of carcinogenicity had not yet been resolved and also because the Johnson (1971) study used by NAS does not provide enough information for a complete judgment of its adequacy.

VII. ANALYTICAL METHODS

- Analysis of picloram is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated acid pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is acidified. The compounds are extracted with ethyl ether using a separatory funnel. The derivatives are hydrolyzed with potassium hydroxide and extraneous organic material is removed by a solvent wash. After acidification, the acids are extracted and converted to their methyl esters using diazomethane as the derivatizing agent. Excess reagent is removed, and the esters are determined by electron-capture (EC) gas chromatography. This method has been validated in a single laboratory, and estimated detection limits have been determined for analytes in this method, including picloram. The estimated detection limit is 0.14 ug/l.

VIII. TREATMENT TECHNOLOGIES

- No information was found on treatment technologies capable of effectively removing picloram from contaminated water.

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*Confidential Business Information.

August, 1988

PROMETON

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

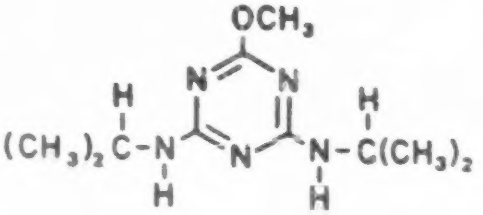
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1610-18-0

Structural Formula



2,4-bis(isopropylamino)-6-methoxy-s-triazine

Synonyms

- Prometon; Gesafram 50; Ontracic 800; Primatol 25E; Pramitol; Methoxypropazine (Meister, 1983).

Uses

A nonselective herbicide that controls most perennial broadleaf weeds and grasses (Meister, 1983).

Properties (Meister, 1983; TDB, 1985; CHEMLAB, 1985)

Chemical Formula	$C_{10}H_{19}N_5O$
Molecular Weight	225.34
Physical State (25°C)	White crystals
Boiling Point	--
Melting Point	91 to 92°C
Density	1.088 g/cm^3
Vapor Pressure (20°C)	2.3 x 10^{-6} mm Hg
Specific Gravity	--
Water Solubility (20°C)	750 mg/L
Log Octanol/Water Partition Coefficient	-1.06 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Prometon has been found in 386 of 1,419 surface water samples analyzed and in 36 of 746 ground water samples (STORET, 1988). Samples were collected at 250 surface water locations and 250 ground water locations, and prometon was found in 12 states. The 85th percentile of all nonzero samples was 0.6 ug/L in surface water and 50 ug/L in ground water sources. The maximum concentration found was 8.5 ug/L in surface water and 250 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Prometon residues resulting from agricultural practice have been detected in California ground waters at 0.21-80 ppb (Eiden, 1987).

Environmental Fate

- Prometon is stable to hydrolysis at pH 5, 7, and 9 at 25°C for 40 days (Ciba-Geigy, 1985a).
- Prometon in aqueous solution was stable to natural sunlight for 2 weeks (Ciba-Geigy, 1985b).
- Prometon has the potential to leach through soil, based on adsorption/desorption tests and soil thin-layer chromatography (TLC). K_d's for five soils were: sandy loam (2.61), silt loam (2.90), silty clay loam (2.40), silt loam (1.20) and sand (0.398); organic matter content ranged from 0.8 to 5% (Ciba-Geigy, 1985c).
- R_f values for soil thin layer chromatography (TLC) plates of five soils put prometon in Class 4 (Very Mobile), Class 3 (Intermediate Mobile), and Class 2 (Low Mobility). Prometon was very mobile in a Mississippi silt loam and Plainfield sand, intermediately mobile in a Hagerstown silty clay loam and Dubuque silt loam, and had low mobility in a California sandy loam (Ciba-Geigy, 1985d).
- In field dissipation studies, prometon was shown to have a half-life >459 to 1,123 days at 3 different sites. Residues were found at all depths sampled, down to 18 inches. There was no deeper sampling. At 2 out of 3 sites, dealkylated prometon was found at the 0- to 18-inch depth (Ciba-Geigy, 1986)

III. PHARMACOKINETICS

Absorption

- Prometon is rapidly absorbed from the gastrointestinal tract. Based on the radioactivity recovered in the urine and feces, prometon is completely absorbed within 72 hours in the rat (Bakke et al., 1967).

Distribution

- Seventy-two hours after intragastric intubation of ^{14}C-prometon in rats, no detectable levels of radioactivity were found in any of the tissues examined (Bakke et al., 1967).

Metabolism

- Eleven metabolites of prometon have been identified in the urine of rats treated with ^{14}C-prometon. 2-Methoxy-4,6-diamino-S triazine and ammeline represented 14% and 31%, respectively, of the radiolabel excreted in the urine (Ciba-Geigy, 1971).

- Based on the metabolites formed, triazine ring cleavage apparently does not occur during prometon metabolism (Ciba-Geigy, 1971).

Excretion

- Excretion of prometon and/or its metabolites in rats was most rapid during the first 24 hours after administration of ^{14}C-prometon and decreased to trace amounts at 72 hours. The radioactivity was quantitatively excreted in the urine (91%) and feces (9%) within 72 hours after dosing with ^{14}C-prometon (Bakke et al., 1967).

IV. HEALTH EFFECTS

Humans

- No information on the health effects of prometon in humans was found in the available literature.

Animals

Short-term Exposure

- The acute oral LD_{50} value for prometon ranges from 1,750 to 2,980 mg/kg in rats and is 2,160 mg/kg in mice (Meister, 1983; NIOSH, 1985).

- The acute inhalation LC_{50} value in rats is >3.6 mg/L for 4 hours (Meister, 1983).

- Long-Evans rats of both sexes (five/sex/dose) were fed a diet containing 0, 10, 30, 100, 300, 600, 1,000, 3,000, 6,000 or 10,000 ppm prometon [technical, 97% active ingredient (a.i.)] for 4 weeks (Kileen et al., 1976a). This corresponds to doses of 0, 0.5, 1.5, 5, 15, 30, 50, 150, 300, or 500 mg/kg/day, assuming 1 ppm in the diet corresponds to 0.05 mg/kg/day (Lehman, 1959). Rats fed 3,000 or more ppm prometon showed a reduction in body weight during the treatment period; at 6,000 or 10,000 ppm (300 or 500 mg/kg/day) the reduction in body weight was statistically significant ($p < 0.05$ and 0.01, respectively). At 1,000 ppm or less, mean body weight of both males and females were comparable to controls. Gross pathology performed at the time of sacrifice did not show any compound-related effects. The No-Observed-Adverse-Effect Level (NOAEL) and Lowest-Observed-Adverse-Effect Level (LOAEL) identified in this study are 3,000 and 6,000 ppm (150 and 300 mg/kg/day), respectively.

- Beagle dogs (one/sex/dose) were administered 100, 300 or 3,000 ppm prometon (technical) in the diet (2.5, 7.5 or 75 mg/kg/day, assuming 1 ppm in the diet is equivalent to 0.025 mg/kg/day; Lehman, 1959) for 2 weeks after which the 100- and 300-ppm doses were changed to 1,000 and 2,000 ppm (25 and 50 mg/kg/day) for the next 2 weeks (Killeen et al., 1976b). Dogs that consumed 3,000 ppm showed a decrease in body weight and food consumption. The body weight of the females receiving 1,000 or 2,000 ppm (25 or 50 mg/kg/day) was also decreased slightly; food consumption was also slightly lower for the females receiving 2,000 ppm prometon (50 mg/kg/day). At 300 ppm and less, the body weight and food consumption for both males and females were comparable to those of the controls. The NOAEL and LOAEL identified in this study are 300 and 1,000 ppm (7.5 and 25 mg/kg/day), respectively.

Dermal/Ocular Effects

- Prometon is a minimal dermal irritant (Meister, 1983). Barely perceptible erythema was observed in rabbits exposed to 500 mg prometon (97%) applied to one abraided and one intact site for 24 hours. At 2,000 mg/kg, mild edema and slight desquamation was also observed (Ciba-Giegy, 1976).

Long-term Exposure

- Sprague-Dawley rats (30/sex/group) were fed a diet containing technical prometon (98% active ingredient) at levels of 0, 10, 50, 100 or 300 ppm for 90 days (Johnson and Becci, 1982). Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to approximately 0, 0.5, 2.5, 5 or 15 mg/kg/day. Although female rats exposed to 300 ppm showed an increase in mean absolute weight of the kidneys, this was considered of no toxicological significance, since the relative kidney to body weight ratios were not changed. The NOAEL identified in this study is, therefore, 300 ppm (15.0 mg/kg/day, the highest dose tested).

Reproductive Effects

- Prometon (technical, 98% a.i.) in corn oil was administered to Charles River rats (25/dose) via gavage at levels of 0, 36, 120 or 360 mg/kg/day from days 6 through 15 of gestation (Florek et al., 1981). Rats treated with 120 or 360 mg/kg/day gained less body weight than the controls during treatment; body weight gain in the 36-mg/kg/day group was similar to that of the controls. Rats in all dosage groups exhibited excessive salivation. Increased respiratory rate and lacrimation were also seen in the 360-mg/kg/day group. No effects on implantation, litter size, fetal viability, resorption, average fetal body weight or gross external, soft tissue or skeletal variation in the fetuses were observed at any dose level. This study identified a maternal NOAEL of 36 mg/kg/day and a maternal LOAEL of 120 mg/kg/day.

- New Zealand White rabbits (16/dose) administered prometon at dose levels of 0, 0.5, 3.5 or 24.5 mg/kg/day (98% a.i.) from days 6 through 30 of gestation showed reduced pregnancy rates at all dosage levels (Lightkep et al., 1982). Pregnancy occurred in 16, 13, 13 and 11 rabbits given

0, 0.5, 3.5 and 24.5 mg/kg/day, respectively. Anorexia and excess lacrimation were observed more frequently in the high-dose group. Maternal body weight was significantly retarded during treatment in the 24.5-mg/kg/day group. The maternal NOAEL identified in this study is 3.5 mg/kg/day and the maternal LOAEL is 24.5 mg/kg/day.

Developmental Effects

- Florek et al. (1981) reported no effects on fetal viability, resorption, average fetal body weight or gross external, soft tissue or skeletal variations in the fetuses of Charles River rats (25/dose) administered prometon via gavage at levels of 0, 36, 120 or 360 mg/kg/day (98% a.i.) in corn oil. Maternal weight gain was depressed in rats administered 120 and 360 mg/kg/day. A teratogenic NOAEL of 360 mg/kg/day (the highest dose tested) and a maternal-toxicity NOAEL of 36 mg/kg/day were identified.

- Lightkep et al. (1982) observed no gross, soft tissue or skeletal variations in fetuses of New Zealand White rabbits (16/dose) administered prometon at dose levels of 0, 0.5, 3.5 or 24.5 mg/kg/day (98% a.i.) on days 6 through 30 of gestation. A teratogenic NOAEL of 24.5 mg/kg/day (the highest dose tested) and a maternal-toxicity NOAEL of 3.5 mg/kg/day were identified.

Mutagenicity

- No information on the mutagenicity of prometon was found in the available literature.

Carcinogenicity

- No information on the carcinogenicity of prometon was found in the available literature.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\underline{\quad}\ \text{L/day})} = \underline{\quad}\ \text{mg/L}\ (\underline{\quad}\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000, or 10,000) in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for prometon. It is therefore recommended that the DWEL value adjusted for the 10-kg child (0.2 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

Prometon has been the subject of several acute toxicity assays including four-week feeding studies in rats and dogs, and developmental toxicity studies with rats and rabbits in which pregnant animals were dosed for 10 days during gestation (Killeen et al., 1976a; Florek et al., 1981; Killeen et al., 1976b; Lightkep et al., 1982). The only toxic effect consistently observed in these studies was reduced weight gain in treated animals. Although of appropriate duration, these studies were judged unacceptable for deriving the Ten-day HA; fluctuations in weight gain may not be an appropriately sensitive end point of toxicity for the basis of the HA. For this reason, it is recommended that the DWEL, adjusted for a 10-kg child (0.2 mg/L, calculated below) be used as a conservative estimate of the Ten-day HA value for prometon.

Longer-term Health Advisory

The only species to be tested in subchronic studies of prometon toxicity was the rat. In the study by Johnson and Becci (1982), rats were fed a diet containing 0, 10, 50, 100 or 300 ppm prometon (0, 0.5, 2.5, 5 or 15 mg/kg/day) for 90 days. A NOAEL of 15 mg/kg/day (the highest dose tested) was identified. Rats were also tested in a 4-week feeding study in which a a NOAEL of 100 mg/kg and a LOAEL of 300 mg/kg/day were identified (Killeen et al. 1976a). Although the NOAEL from the subchronic study can be used as a basis for the Longer-term HA, lower NOAELs have been identified in acute studies of other species (3.5 mg/kg/day, rabbit, Lightkep et al., 1982; 7.5 mg/kg/day, dog, Killeen et al, 1976b). It is therefore recommended that the DWEL (0.5 mg/L, calculated below) and the DWEL, adjusted for the 10-kg child (0.2 mg/L, calculated below) be used as conservative estimates of the Longer-term HA for the adult and child, respectively.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

No suitable chronic or lifetime studies were available for the calculation of a Lifetime HA for prometon. Effects on body weight gain have been observed in acute studies at doses as low as 120 mg/kg/day for rats (Florek et al., 1981), 25 mg/kg/day for dogs (Killeen et al., 1976b), and 24.5 mg/kg/day for rabbits (Lightkep et al., 1982). One subchronic study was available (Johnson and Becci, 1982). In this study, rats were fed diets containing 0, 10, 50, 100, or 300 ppm prometon for 90 days. No toxic effects were observed at any of the dose levels tested, and a NOAEL of 15 mg/kg/day was identified. This value may be a conservative estimate of the NOAEL for rats; a NOAEL of 150 mg/kg was identified from the 4-week feeding study by Killeen et al. (1976a). Taking into consideration both the acute and subchronic test results, the study of Johnson and Becci (1982) has been selected to serve as the basis for determination of the RfD.

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(15 \text{ mg/kg/day})}{(1{,}000)} = 0.015 \text{ mg/kg/day}$$

where:

15 mg/kg/day = NOAEL, based on the absence of effects on the absolute weight of the kidneys and on the mean kidney-to-brain ratios in rats exposed to prometon in the diet for 90 days.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.015 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.5 \text{ mg/L } (500 \text{ ug/L})$$

where:

0.015 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

The DWEL, modified for the 10-kg child and rounded to one significant figure, is derived as follows:

$$\text{DWEL}_{\text{child}} = \frac{(0.015\ \text{mg/kg/day})\ (10\ \text{kg})}{(1\ \text{L/day})} = 0.2\ \text{mg/L}\ (200\ \text{ug/L})$$

where:

0.015 mg/kg/day = RfD.

10 kg = assumed body weight of a child.

1 L/day = assumed daily water consumption of a child.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = 0.5 mg/L x 20% = 0.1 mg/L (100 ug/L)

where:

0.5 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No carcinogenicity studies were found in the literature searched.
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of prometon.
- Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), prometon may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- No information was found in the available literature on other existing criteria, guidelines and standards pertaining to prometon.

VII. ANALYTICAL METHODS

- Analysis of prometon is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen-phosphorus detector. This method has been validated in a single laboratory, and the estimated detection limit for prometon is 0.3 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Whittaker (1980) experimentally determined the adsorption isotherms for prometon on granular activated carbon (GAC).
- One study (Rees and Au, 1979) reported 95% removal efficiency when prometon-contaminated water was passed over a 1 x 20 cm column packed with resin.

- Available data indicate that GAC adsorption and resin adsorption will remove prometon from water (Whittaker, 1980; Rees and Au, 1979). However, selection of an individual technology or a combination of technologies to attempt prometon removal from water must be based on a case-by-case technical evaluation and an assessment of the economics involved.

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August, 1988

PRONAMIDE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

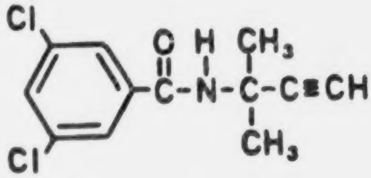
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 23950-58-5

Structural Formula



3,5-Dichloro(N-1,1-dimethyl-2-propynyl)benzamide

Synonyms

- Kerb®; Kerb® 50W; Propyzamide; RH315 (Meister, 1983).

Uses

- Pronamide is used as an herbicide for pre- or postemergence weed and grass control in small, seeded legumes grown for forage or seed, southern turf, direct seeded or transplanted lettuce, endive, escarole, woody ornamentals, nursery stock and Christmas trees (Meister, 1983).

Properties (NIOSH, 1985; TDB, 1985)

Chemical Formula	$C_{12}H_{11}Cl_2ON$
Molecular Weight	256.14
Physical State (25°C)	White crystals
Boiling Point	--
Melting Point	154 to 156°C
Density	--
Vapor Pressure (25°C)	8.5×10^{-5} mm Hg
Specific Gravity	0.48 gm/cc
Water Solubility	15 ppm (mg/L)
Log Octanol/Water Partition Coefficient	3.05 to 3.27
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Pronamide has been found in 20 of 391 ground water samples analyzed, all in California (STORET, 1988). No surface water samples were collected. Ground water samples were collected 391 locations. The concentration of all samples found was 1.0 ug/L. STORET contains no information on surface water sampling for pronamide. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- ^{14}C-Pronamide (100% radiopurity) at 1.5 ppm hydrolyzes very slowly (10% of applied material) in sterile, deionized water buffered to pH 5, 7, and 9 and incubated at 20°C for 28 days in the dark (Rohm and Haas Bristol Research Laboratories, 1973). The following minor hydrolysis products were identified: RH-24,644 (2-(3,5-dichlorophenyl)-4,4-dimethyl-5methyleneoxazoline); RH-24,580 (3,5-dichloro-N-(1,1-dimethylacetonyl) benzamide); and RH-25,891 (2-(3,5-dichlorophenyl)-4,4-dimethyl-5-hydroxymethyl-oxazoline). Similar results were obtained in other hydrolysis studies (Rohm and Haas Bristol Research Laboratories, 1970).

- Pronamide has a half-life of 10 to 120 days in aerobic soils (Fisher, 1971; Walker, 1976; Walker and Thompson, 1977; Walker, 1978; Hance, 1979;). Complete experimental conditions and purity were not specified, and/or a formulated product was applied. The degradation rate does not appear to depend upon soil texture. However, increasing soil temperature, and to a lesser extent, soil moisture and pH enhance pronamide degradation. The major degradates are RH-24,580 and RH-24,644. Soil sterilization greatly reduced the degradation rate of pronamide. Pronamide (at a recommended application rate of 0.5 to 2 lb/A) does not inhibit the growth or CO_2 evolution of bacteria and fungi (Lashen, 1970).

- Pronamide is moderately mobile in soils ranging in texture from loamy sand to clay based on preliminary soil column and adsorption/desorption tests (Walker and Thompson, 1977; Rohm and Haas Company, 1971; Fisher and Satterthwaitte, 1971). The two major degradates of pronamide (RH-24,580 and RH-24,644) are mobile in sand and clay soils (Fisher, 1973). The mobility of pronamide and its two major degradates tends to decrease as the organic matter content, clay content and cation exchange capacity of the soil increases.

- The dissipation rate of pronamide from terrestrial field sites is quite variable, with half-lives ranging from 10 to 90 days (Benson, 1973; Walker, 1976; Hance et al., 1978a,b; Kostowska et al., 1978; Walker, 1978; Zandvoort et al., 1979). Data are insufficient to determine the effect, if any, of meteorological conditions or the role leaching may play in pronamide dissipation.

- The environmental fate of pronamide is the subject of several unpublished, undated reports (Cummings and Yih; Fisher and Cummings; Rohm and Haas; Satterthwaite and Fisher; Yih).

III. PHARMACOKINETICS

Absorption

- No information on the absorption of pronamide was found in the available literature. Data on the systemic toxicity of oral doses indicate that pronamide is absorbed following ingestion.

Distribution

- No information on the distribution of pronamide was found in the available literature.

Metabolism

- About 54 and 0.6% of the radioactivity was recovered as unmetabolized Kerb® in the feces and urine, respectively, of rats treated orally with (^{14}C-carbonyl)-pronamide (dose not specified) (Yih and Swithenbank, undated). The major metabolite in the feces was 2-(3,5-dichlorophenyl)-4,4-dimethyl-5-hydroxymethyloxazoline (15%), and the major metabolites in the urine were α-(3,5-dichlorobenzamido) isobutyric acid (22.4%), β-(3,5-dichlorobenzamido)-α-hydroxy-β methyl-butyric acid (19.2%), and two unknown metabolites (24.1 and 16.7%).

- Unmetabolized Kerb® did not appear in the urine of cows treated orally with (^{14}C-carbonyl) Kerb®; the major metabolite was β-(3,5-dichlorobenzamido)-α-hydroxy-β-methyl-butyric acid (71.4%)(Yih and Swithenbank, undated).

Excretion

- After oral ingestion of radiolabeled Kerb® by rats, unmetabolized Kerb® accounted for 54 and 0.6% of the radioactivity recovered in feces and urine, respectively. In the cow, oral ingestion of Kerb® produced no unmetabolized Kerb® in the urine (Yih and Swithenbank, undated).

IV. HEALTH EFFECTS

Humans

- No information on the health effects of pronamide in humans was found in the available literature.

Animals

Short-term Exposure

- The acute oral LD_{50} in rats for pronamide (technical) is in the range of 5,620 mg/kg bw (Meister, 1984) to 16,000 mg/kg bw (Powers, 1970).

Dermal/Ocular Effects

- Pronamide is not a primary dermal irritant to albino rabbits. In two separate studies, an aqueous paste of 500 mg pronamide [50% active ingredient (a.i.)] was applied to the skin of six rabbits for 24 hours (Powers, 1970; Regel, 1972). No signs of irritation were observed by Powers (1970). Twenty-four hours after exposure, Regel (1972) observed erythema, which subsided at 72 hours.

- Powers (1970) administered 100 mg of Kerb® (50% a.i.) in the conjunctival sac of 12 rabbits. Eye irritation and chemosis were noted at 24 hours but disappeared by day 7, as confirmed by fluorescein examination.

Long-term Exposure

- Charles River CD rats (10/sex/dose) were fed a diet containing 0, 50, 150, 450, 1,350 or 4,050 ppm pronamide (100% a.i.) for 3 months (Larson and Borzelleca, 1967a). These levels correspond to 0, 2.5, 7.5, 22.5, 67.5 or 202.5 mg/kg/day, respectively, assuming 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959). Significant body weight depression was observed at the 4,050 ppm dose level. Initial significant body weight depression also occurred in the rats fed 1,350 ppm, but disappeared on continued feeding. At the 150 ppm dose, absolute and relative liver weights in females were significantly higher than in controls; no histological lesions were seen, and no dose-related trend was observed for this increase in relative liver weight. Individual data were not presented for organ weights and several other parameters, clinical observations were not presented and analytical determination of the test compound was not reported. The No-ObservedAdverse-Effect Level (NOAEL) identified in this study was 2.5 mg/kg/day.

- Beagle dogs (10 months old; one/sex/dose) were fed a diet containing 0, 450, 1,350 or 4,050 ppm pronamide (100% a.i.) for 3 months (Larson and Borzelleca, 1967b). These levels correspond to approximate doses of 0, 11, 34 or 101 mg/kg/day, assuming 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959). A decrease in weight gain and food consumption and an increase in serum alkaline phosphatase, liver weight and liver-to-body weight ratios, as compared to controls, were seen in the animals dosed at 4,050 ppm. No histological changes were seen in the livers. The hematological and urinalysis findings were within normal ranges. The NOAEL identified in this study was 34 mg/kg/day.

- In a 2-year feeding study in beagle dogs (four/sex/dose) the addition of pronamide (97% a.i.) to the diet at dose levels of 0, 30, 100 or 300 ppm (0, 0.75, 2.5 or 7.5 mg/kg/day, assuming 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day; Lehman, 1959) caused no adverse effects at any of the doses tested (Larson and Borzelleca, 1970b). A NOAEL of 7.5 mg/kg/day (the highest dose tested) was identified in this study.

- Smith (1974) administered Kerb® (97% a.i.) to 6-week-old (C57 BL16 x C3H Anf)F_1 male and female mice (100/sex/dose), for 78 weeks at dietary pronamide concentrations of 0, 1,000 or 2,000 ppm (0, 150 or 300 mg/kg/day, assuming 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day; Lehman, 1959). Male and female mice that ingested 2,000 ppm gained significantly less weight ($p < 0.05$); males also exhibited adenomatous hyperplasia, degeneration, hyperplasia, intrahepatic cholestasis, necrosis and/or fatty changes of the liver. Liver weights were significantly increased over controls for males and females in both treatment groups. Based on this information, a Lowest-Observed-Adverse-Effect Level (LOAEL) of 1,000 ppm (150 mg/kg/day) was identified.

- Newberne et al. (1982) administered pronamide (94% a.i.) to male B6C3F_1 mice at dose levels of 0, 13, 70, 329 or 2,260 ppm (0, 2, 10, 49 or 340 mg/kg/day, assuming 1 ppm in the diet of mice is equivalent 0.15 mg/kg/day; Lehman, 1959) for up to 24 months. Another group was fed 2,500 ppm pronamide for 6 months. The mean body weight of the mice fed 2,500 ppm was significantly depressed at 14 days and thereafter throughout the study. At the 24-month sacrifice, the mean body weight of this group was approximately 70% of the control group. Survival of the mice was unaffected. The highest dose level (2,500 ppm) resulted in liver lesions including bile duct hyperplasia, parenchymal cell hypertrophy, parenchymal cell necrosis, hyperplasia and cholestasis at all time periods examined. Based on this information, a NOAEL of 329 ppm (49 mg/kg/day) was identified.

Reproductive Effects

- Costlow and Kane (1985) administered pronamide (technical, 97% pure) to New Zealand White rabbits (16/dose) at doses of 0, 5, 20 or 80 mg/kg/day during gestation days 7 to 19. An increased incidence of gross and microscopic liver lesions, one maternal death, five abortions and a significant ($p < 0.05$) decrease in the maternal body weight gain were observed at the 80-mg/kg/day dose. At the 20-mg/kg/day dose, rabbits exhibited anorexia, vacuolation of hepatocytes and a slight decrease in body weight gain. There were no compound-related effects on the incidence of implantations, resorptions, fetal deaths or on fetal body weight at any dose tested. A NOAEL of 20 mg/kg/day was identified based upon the absence of developmental/reproductive effects and a NOAEL of 5 mg/kg/day was identified based upon the absence of maternal toxicity observed at higher doses.

- In a three-generation reproduction study, 20 to 25 albino CD rats were fed a diet containing pronamide (RH-315; 97% a.i.) at dose levels of 0, 30, 100 or 300 ppm (Larson and Borzelleca, 1970c). Assuming 1 ppm in the diet is equivalent to 0.05 mg/kg/day, these levels correspond to doses of 0, 1.5, 5 or 15 mg/kg/day (Lehman, 1959). The authors reported no adverse reproductive effects in parents or pups, but individual animal data were not available to validate the above conclusions. Based on this information a NOAEL of 300 ppm (15 mg/kg/day, the highest dose tested) was identified.

Developmental Effects

- Costlow and Kane (1985) administered pronamide (technical, 97% pure) to New Zealand White rabbits (18/dose) at doses of 0, 5, 20 or 80 mg/kg/day (technical, 97% pure) during gestation days 7 to 19. There were no compound-related effects on the incidence of implantations, resorptions, fetal deaths or on fetal body weight at any dose tested. The NOAEL in this study was 80 mg/kg/day based on the absence of developmental effects at any dose tested. The NOAELs for developmental effects and maternal toxicity, described above, are 20 and 5 mg/kg/day, respectively.

- In a study designed to evaluate fetal development, adult female rats (FDRL) were administered 0, 7.5 or 15 mg/kg/day pronamide by gavage in corn oil from days 6 through 16 of gestation (Vogin, 1971). No adverse effects were reported for the mean number of implantation sites, the number of live or dead fetuses or the mean fetal weight. The authors concluded that pronamide administered orally to rats at doses up to 15 mg/kg/day was not teratogenic. Individual animal data were not available to validate these conclusions, and, therefore, the study was not validated. Based on this information a NOAEL of 15 mg/kg/day (the highest dose tested) was identified.

Mutagenicity

- In a cytogenetic study, pronamide (Kerb®, analytical) administered by intragastric intubation at dose levels of 5, 50 or 500 mg/kg to rats did not produce any aberrations of the bone marrow chromosomes (Fabrizio, 1973).

Carcinogenicity

- In a study evaluating the carcinogenic potential of Kerb®, 6-week-old (C57 BL16 x C3H Anf)F_1 male and female mice (100/sex/dose) were fed pronamide (97% a.i.) in the diet at doses of 0, 1,000 or 2,000 ppm (0, 150 or 300 mg/kg/day, assuming 1 ppm in feed is equivalent to 0.15 mg/kg/day; Lehman, 1959) for 78 weeks (Smith, 1974). Male and female mice that ingested 2,000 ppm gained significantly less weight ($p < 0.05$); the animals also gained slightly less weight at the 1,000-ppm level, but the change was not significant. No increase in tumors was observed for female mice treated with pronamide over controls. For male mice, a total of 35 of the 99 animals in the high-dose group, 21 of the 100 animals in the low-dose group and 7 of the 100 animals in the control group developed hepatic neoplasms, of which 24, 18 and 7 were carcinomas in the high-dose, low-dose and control groups, respectively. A total of 28 of 99 male mice that ingested 2,000 ppm exhibited intrahepatic cholestasis, but did not have carcinomas of the liver.

- In a 2-year study in male B6C3F_1 mice (Newberne et al., 1982), technical pronamide (97%) was fed to the animals (63 animals/dose) at target doses of 0, 20, 100, 500 or 2,500 ppm. Actual measured levels were 0, 13, 70, 329, or 2262 ppm (0, 2, 10, 49 or 340 mg/kg/day assuming 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day). Another group was fed a target dose of 2,500 ppm pronamide for 6 months. The mean body weight of mice fed 2,500 ppm was significantly depressed at 14 days and thereafter throughout the study. At the 24-month sacrifice, the mean body weight of this group was approximately 70% of the control group. Survival of the mice was unaffected. The highest dose (2,500 ppm) resulted in liver lesions, including bile duct hyperplasia, parenchymal cell hypertrophy, parenchymal cell necrosis, hyperplasia and cholestasis at all time periods examined. At 18 months, the 2,500-ppm target dose group had increased parenchymal cell neoplasms, but this was not statistically different from the controls. At 24 months, there was a statistically significant increased incidence of hepatic adenomas and carcinomas in the 500- and 2,500-ppm dose groups. The incidence of hepatic carcinomas was 5/63, 9/63, 12/63, 18/63 and 14/61 in the control, 20-ppm, 100-ppm, 500-ppm and 2,500-ppm groups, respectively. Thus, the liver appears to be the target organ for neoplasia. According to the authors, hypertrophy and hyperplasia are not uncommon in untreated older mice of this strain. However, pronamide tended to shift the onset of these lesions to an earlier age.

° Pronamide in the diet at dose levels of 0, 30, 100 or 300 ppm (0, 1.5, 5 or 15 mg/kg/day, assuming 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day; Lehman, 1959) fed to rats (30/sex/group) for 2 years did not produce any carcinogenic effects (Larson and Borzelleca, 1970a). However, doses used in this study were too low to assess the carcinogenic potential of pronamide.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\underline{\quad\quad} \text{ L/day})} = \underline{\quad\quad} \text{ mg/L } (\underline{\quad\quad} \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000) in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for pronamide. It is therefore recommended that the Longer-term HA value of 0.8 mg/L (800 ug/L) be used at this time as a conservative estimate of the One-day HA value for pronamide.

Ten-day Health Advisory

Toxicity from acute exposure to pronamide has been assessed in three reproductive/developmental toxicity studies. No effects were observed in rats exposed to pronamide via gavage (Vogin, 1972) or in feed (Larson and Borzelleca, 1967b) at doses as high as 15 mg/kg/day. No higher doses were tested in the rat, but higher doses have been tested in the rabbit (Costlow and Kane, 1985). In this study, New Zealand White rabbits were administered pronamide during gestation days 7 through 19 at dose levels of 0, 5, 20 or 80 mg/kg/day. Toxic effects observed at the highest dose include a statistically significant decrease in maternal body weight gain and an increased incidence of gross and microscopic liver lesions. Minor effects on body weight and liver toxicity were observed at the 20-mg/kg/day dose, and a NOAEL of 5 mg/kg/day was identified. This value is similar to the NOAEL used to derive the Longer-term HA (7.5 mg/kg/day; Larson and Borzelleca, 1970b), indicating little difference may exist between doses which cause acute and chronic toxicity. It is therefore recommended that the Longer-term HA value of 0.8 mg/L (800 ug/L), calculated below, be used at this time as a conservative estimate of the Ten-day HA value for pronamide.

Longer-term Health Advisory

Liver toxicity has been observed after both acute and chronic administration of pronamide to experimental animals. Adverse effects on the liver have been observed after acute exposure of rabbits to 80 mg/kg/day via gavage (Costlow and Kane, 1985), subchronic exposure of dogs to 90 mg/kg/day (Larson and Borzelleca, 1967b), and chronic feeding of 300 and 375 mg/kg/day to mice (Smith, 1974; Newberne et al, 1982). Data on rats are equivocal. Signs of hepatoxicity from subchronic exposure (increased liver weight after 90 days' exposure to 7.5 mg/kg/day; Larson and Borzelleca, 1970a) were not observed in a three generation study with doses as high as 15 mg/kg/day (Larson and Borzelleca, 1970c).

These data indicate that there may be little difference between doses which cause acute, subchronic or chronic toxicity. Therefore, it is recommended that the basis for the Lifetime HA be used to derive a conservative estimate of the Longer-term HA. In this study, beagle dogs fed a diet containing pronamide a dose levels of 0, 30, 100 or 300 ppm (0, 0.75, 2.5 or 7.5 mg/kg/day) for two years showed no adverse effects at any of the doses tested. A NOAEL of 7.5 (the highest dose tested) was identified in this study.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term}_{\text{child}} = \frac{(7.5\ \text{mg/kg/day})(10\ \text{kg})}{(100)(1\ \text{L/day})} = 0.8\ \text{mg/L}$$

where:

7.5 mg/kg/day = NOAEL based on the absence of adverse effects in dogs administered pronamide in the diet for 2 years.

10 kg = assumed body weight of a child

1 L/day = assumed daily water consumption of a child.

100 = Uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term}_{\text{adult}} = \frac{(7.5\ \text{mg/kg/day})(70\ \text{kg})}{(100)(2\ \text{L/day})} = 3.0\ \text{mg/L}$$

where:

7.5 mg/kg/day = NOAEL based on the absence of adverse effects in dogs administered pronamide in the diet for 2 years.

70 kg = assumed body weight of an adult

2 L/day = assumed daily water consumption of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Two-year chronic pronamide feeding studies have been performed in three species: the rat (Larson and Borzelleca, 1970a), mouse (Newberne et al., 1982), and dog (Larson and Borzelleca, 1970b). For the rat and dog studies, only low doses were used and no toxic effects were observed. The highest doses tested, 15 mg/kg/day (rat) and 7.5 mg/kg/day (dog), were identified as NOAELs for these studies. Because of deficiencies in the rat study (data on individual animals not provided, insufficient number of animals routinely monitored for clinical chemistry parameters) this study was not validated (U.S. EPA, 1985), and is therefore not acceptable as the basis for the Lifetime HA value. The 2-year study performed on mice (Newberne et al., 1982) was rejected as the basis for the Lifetime HA because of the relative insensitivity of mice to pronamide compared to other species. The NOAEL of 75 mg/kg/day identified in this study was higher than doses causing liver toxicity in subchronic feeding studies in both the rat and dog (Larson and Borzelleca, 1967a,b). Taking all of these studies into consideration, the 2-year feeding study in dogs (Larson and Borzelleca, 1970b) was selected as the basis for determination of the Lifetime HA for pronamide. In this study, beagle dogs fed a diet containing pronamide at dose levels of 0, 30, 100 or 300 ppm (0, 0.75, 2.5 or 7.5 mg/kg/day) for 2 years showed no adverse effects at any of the doses tested. A NOAEL of 7.5 mg/kg/day (the highest dose tested) was identified in this study.

Using a NOAEL of 7.5 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(7.5 \text{ mg/kg/day})}{(100)} = 0.075 \text{ mg/kg/day}$$

where:

7.5 mg/kg/day = NOAEL, based on the absence of adverse effects in dogs administered pronamide in the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.075 \text{ mg/kg/day})\ (70 \text{ kg})}{2 \text{ L/day}} = 2.6 \text{ mg/L} \quad (2{,}600 \text{ ug/L})$$

where:

0.075 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(2.6\text{ mg/L})\ (20\%)}{(10)} = 0.05\text{ mg/L } (50\text{ ug/L})$$

where:

2.6 mg/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), pronamide may be classified Group C: possible human carcinogen. This category is for substances with limited evidence of carcinogenicity in animals in the absence of human data.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- A Provisional Acceptable Daily Intake (PADI) of 0.0750 mg/kg/day and a calculated Theoretical Maximum Residue Concentration (TMRC) of 0.0409 mg/day that utilizes 0.91% of the PADI has been established (U.S. EPA, 1985a).

- Residue tolerances have been established for pronamide and its metabolites in or on raw agricultural commodities that range from 0.02 ppm to 10.0 ppm (U.S. EPA, 1985b).

VII. ANALYTICAL METHODS

- Analysis of pronamide is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen-phosphorus detector. This method has been validated in a single laboratory, and the estimated detection limit for pronamide is 0.76 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Reverse osmosis (RO) is a promising treatment method for pesticide-contaminated water. As a general rule, organic compounds with molecular weights greater than 100 are candidates for removal by RO. Larson et al. (1982) report 99% removal efficiency of chlorinated pesticides by a thin-film composite polyamide membrane operating at a maximum pressure of 1,000 psi and at a maximum temperature of 113°F. More operational data are required, however, to specifically determine the effectiveness and feasibility of applying RO for the removal of pronamide from water. Also, membrane adsorption must be considered when evaluating RO performance in the treatment of pronamide-contaminated drinking water supplies.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

PROPACHLOR

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

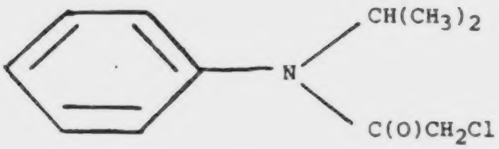
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1918-16-7

Structural Formula



2-chloro-N-isopropylacetinilide

Synonyms/Common Formulations

- Bexton; Prolex; Ramrod (Meister, 1983).

Uses

- Selective postemergence herbicide used for control of many grasses and certain broadleaf weeds (Meister, 1983).

Properties (Rao and Davidson, 1982; HSDB, 1986)

Chemical Formula	$C_{11}H_{14}ClNO$
Molecular Weight	211.69
Physical State (room temp.)	White crystalline solid
Boiling Point	110°C at 0.03 mm HG
Melting Point	77 to 78°C
Density (25°C)	1.13 g/mL
Vapor Pressure (25°C)	7.9×10^{-5} mm Hg
Specific Gravity	1.242
Water Solubility (20°C)	580 mg/L
Log Octanol/Water Partition Coefficient	2.30
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Propachlor has been found in 34 of 1,690 surface water samples analyzed and in 2 of 99 ground water samples (STORET, 1988). Samples were collected at 475 surface water locations and 94 ground water locations, and propachlor was found in eight states. The 85th percentile of all nonzero samples was 2 ug/L in surface water and 0.12 ug/L in ground water sources. The maximum concentration found was 10 ug/L in surface water and 0.12 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out

of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Propachlor is degraded in aerobic soils in the laboratory and in the field with half-lives of 2 to approximately 14 days, when the soils are treated with propachlor at recommended application rates. However, degradation was relatively slower in soil treated at 500 ppm, and 90% of the applied material remained after 21 days (Registrant CBI data).

- The major propachlor degradates produced under aerobic soil conditions are [(1-methylethyl)phenylamino]oxoacetic acid and [(2-methylethyl)-phenylamino]-2-oxoethane sulfonic acid. These degradates are recalcitrant to further degradation in soil under anaerobic conditions. The half-life of propachlor in anaerobic soil is <4 days (Registrant CBI data).

- Propachlor degrades very slowly (84.5% remaining after 30 days) in lake water (Registrant CBI data).

- Propachlor is moderately mobile to very mobile in soils ranging in texture from sand to clay. Mobility appears to be correlated with clay content and to a lesser degree with organic matter content and CEC. Aged ^{14}C-propachlor residues were mobile in a silt loam soil (Registrant CBI data).

- The rapid degradation of low levels of propachlor in soils is expected to result in a low potential for groundwater contamination by propachlor degradates. ^{14}C-Propachlor residues are taken up by rotated corn planted under confined conditions; <3% of the radioactivity remained in soil at the time of planting (Registrant CBI data).

III. PHARMACOKINETICS

Absorption

- No direct data on rate of gastrointestinal absorption of propachlor were found in the available literature. Based on recovery studies, propachlor appears to be rapidly absorbed by the oral route of administration. An estimated 68% of a single dose of 10 mg of ring-labeled ^{14}-C propachlor administered to 12 rats was recovered in urine 56 hours after compound administration (Malik, 1986). These results are supported by other studies in which 54 to 64% (Lamoureux and Davison, 1975) and 68.8% (Bakke et al., 1980) of the administered dose was recovered in urine 24 hours and 48 hours after dose administration, respectively.

Distribution

- Fifty-six hours following oral administration of 10 mg of ring-labeled ^{14}C-propachlor (purity not specified) to rats, no detectable levels of radioactivity were identified in any tissue samples (Malik, 1986).

Metabolism

- Metabolism of propachlor occurs by initial glutathione conjugation followed by conversion via the mercapturic acid pathway; oxidative metabolism also occurs (Lamoureux and Davison, 1975; Malik, 1986).

- Eleven urinary metabolites have been identified as the result of propachlor metabolism in rats. The primary metabolic end products of propachlor are mercapturic acid and glucuronic acid conjugates (approximately 20 to 25%), methyl sulfones (30 to 35%), and phenols and alcohols (Lamoureux and Davison, 1975; Malik, 1986).

Excretion

- Propachlor (purity not specified) was excreted in the form of metabolites in the urine (68%) and feces (19%) of rats within 56 hours after dosing with ring-labeled ^{14}C-propachlor. Methyl sulfonyl metabolites accounted for 30 to 35% of the administered dose (Malik, 1986).

- In studies with germ-free rats, 98.6% of the administered dose (not specified) for propachlor (purity not specified) was identified in the urine (68.8%) and feces (32.1%) within 48 hours. The major metabolite was mercapturic acid conjugate, which accounted for 66.8% of the administered dose (Bakke et al., 1980).

IV. HEALTH EFFECTS

Humans

- Schubert (1979) reported a case study in which occupational exposure to propachlor for 8 days resulted in erythemato-papulous (red pimply) contact eczema on the hands and forearms.

Animals

Short-term Exposure

- The acute oral LD_{50} values for technical-grade (approximately 96.5%) and wettable powder (WP) (65%) propachlor range from 1,200 to 4,000 mg/kg in rats. Technical-grade and wettable powder propachlor both produced a low LD_{50} value of 1,200 mg/kg (Keeler et al., 1976; Heenehan et al., 1979; Auletta and Rinehart, 1979; Monsanto, (undated).

- Beagle dogs (two/sex/dose) were administered propachlor (65% WP) in the diet for 90 days at dose levels of 0, 1.3, 13.3 or 133.3 mg/kg/day

(Wazeter et al., 1964). Body weight, survival rates, food consumption, behavior, general appearance, hematology, biochemical indices, urinalysis, histopathology and gross pathology were comparable in treated and control animals. The No-Observed-Adverse-Effect Level (NOAEL) identified for this study is 133.3 mg/kg/day (the highest dose tested).

- Naylor and Ruecker (1985) fed propachlor (96.1% active ingredient [a.i.]) to beagle dogs (six/sex/dose) in the diet for 90 days at dose levels of 0, 100, 500 or 1,500 ppm. Based on the assumption that 1 ppm in food is equivalent to 0.025 mg/kg/day (Lehman, 1959), these doses are equivalent to 0, 2.5, 12.5 or 37.5 mg/kg/day. Clinical signs, ophthalmoscopic, clinicopathologic, gross pathology and histopathologic effects were comparable for treated and control groups. The reduction in food consumption and concomitant reductions in body weight gain at all test levels were considered by the author to be due to poor diet palatability. Based on these responses, a NOAEL of 1,500 ppm - the highest dose tested (37.5 mg/kg/day) was identified.

Dermal/Ocular Effects

- The acute dermal LD_{50} value of technical propachlor and WP (65% propachlor) in the rabbit ranges from 380 mg/kg to 20 g/kg (Keeler et al., 1976; Monsanto, undated; Braun and Rinehart, 1978). Wettable powder produced the lowest LD_{50} in rabbits (380 mg/kg); the lowest LD_{50} produced by technical propachlor was between 1,000 and 1,260 mg/kg in rabbits.

- Propachlor (94.5% a.i.) (1 g/mL) applied to abraded and intact skin of New Zealand White rabbits (three/sex) for 24 hours produced erythema and slight edema at treated sites 72 hours post-treatment (Heenehan et al., 1979).

- Heenehan et al. (1979) instilled single applications (0.1 cc) of propachlor into one eye of tested New Zealand rabbits for 30 seconds. Corneal opacity with stippling and ulceration, slight iris irritation, conjunctival redness, chemosis, discharge and necrosis were reported at 14 days. Similar responses were reported by Keeler et al. (1976) for a corresponding observation period and by Auletta (1984) during 3 to 21 days post-treatment.

Long-term Exposure

- Albino rats (25/sex/dose) administered 0, 1.3, 13.3 or 133.3 mg/kg/day propachlor (65% WP = 65% a.i.) in the diet for 90 days showed decreased weight gain (10 to 12% less than control levels) in and increased liver weights in both sexes (10% greater than control levels) at 133.3 mg/kg/day (the highest dose tested) (Wazeter et al., 1964). The body and liver weights of rats of both sexes that received the low dose and mid dose were comparable to control levels. Survival, biochemical indices, hematology, urinalysis, gross pathology and histopathology did not differ significantly between treated and control groups. The NOAEL identified in this study is 13.3 mg/kg/day. The Lowest-Observed-Adverse Effect-Level (LOAEL) is 133.3 mg/kg/day (the highest dose tested).

- **Reyna et al.** (1984a) administered propachlor (96.1% a.i.) to rats (30/sex/dose) in the diet for 90 days at mean dose levels of 0, 240, 1,100 or 6,200 ppm. Assuming that 1 ppm is equivalent to 0.05 mg/kg/day, these concentrations correspond to 0, 12, 55 or 310 mg/kg/day (Lehman, 1959). Body weights and food consumption were significantly decreased (no p value specified) at 55 mg/kg/day and 310 mg/kg/day in both sexes. Final body weights for females were 7 and 36% less than controls at the mid- and high-dose levels, respectively. In males, final body weights were 8 and 59% less than control levels for mid- and high-dose levels, respectively. However, histopathological examination showed no changes. Mid- and high-dose levels produced increased platelet counts, decreased white blood cell counts and mild liver cell dysfunction. Mild hypochromic, microcytic anemia was reported at the high dose. A NOAEL of 12 mg/kg/day can be identified for this study.

- Albino mice (30/sex/dose) were fed propachlor (96.1% a.i.) in the diet for 90 days at mean dose levels of 0, 385, 1,121 or 3,861 ppm (Reyna et al., 1984b). Based on the assumption that 1 ppm in food is equivalent to 0.15 mg/kg/day (Lehman, 1959), these doses correspond to 0, 58, 168 or 579 mg/kg/day. Reduced body weight gain, decreased white blood cell count, liver and kidney weight changes and increased incidences of centrolobular hepatocellular enlargement were reported at the mid (168 mg/kg/day) and high (579 mg/kg/day) doses when compared to controls. Based on these responses, a NOAEL of 385 ppm (58 mg/kg/day) can be identified.

Reproductive Effects

- No information on the reproductive effects of propachlor was found in the available literature.

Developmental Effects

- Miller (1983) reported no signs of maternal toxicity in New Zealand female rabbits (16/dose) that were administered propachlor (96.5%) orally by gavage at doses of 0, 5, 15 or 50 mg/kg/day on days 7 to 19 of gestation. Statistically significant increases in mean implantation loss with corresponding decreases in the mean number of viable fetuses were reported at 15 and 50 mg/kg/day when compared to controls. Two low-dose and one mid-dose rabbit aborted on gestation days 22 to 25. These effects, however, do not appear to be treatment-related since no abortions occurred in the high-dose animals. No treatment-related effects were present in the 5-mg/kg/day group (the lowest dose tested). The authors reported that the maternal and embryonic NOAELs were 50 and 5 mg/kg/day, respectively.

- Schardein et al. (1982) administered technical propachlor orally by gavage to rats (25/dose) at dose levels of 0, 20, 60 or 200 mg/kg/day during days 6 to 19 of gestation. There were no adverse fetotoxic or maternal effects reported at any dose level. Based on this information, the NOAEL identified in this study was 200 mg/kg/day (the highest dose tested).

Mutagenicity

- Technical propachlor was not genotoxic in assays of *Salmonella typhimurium* with or without plant and animal activation; however, genotoxic activity was reported in yeast assays (*Saccharomyces cerevisiae*) at 1.3 x 10^{-3} M and 3 mg per plate after plant activation (Plewa et al., 1984).

- In a cytogenic study, propachlor administered by intraperitoneal injection at dose levels of 0.05, 0.2 or 1.0 mg/kg to F344 rats did not induce chromosomal aberrations in bone marrow cells (Ernst and Blazak, 1985).

- Gene mutation was not detected in assays employing Chinese Hamster Ovary (CHO) cells at levels up to 60 ug/ml. Propachlor was cytotoxic at levels of 40 ug/ml and higher (Flowers, 1985). Primary rat hepatocytes exposed to 0.1 to 5,000 ug/mL technical-grade propachlor showed no effect on unscheduled DNA synthesis when compared to controls (Steinmetz and Mirsalis, 1984).

Carcinogenicity

- No information was found in the available literature to evaluate the carcinogenic potential of propachlor. However, several chemicals analogous to this compound, i.e., alachlor and acetochlor, were found to be oncogenic in two animal species.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for propachlor. It is therefore recommended that the Ten-day HA value for the 10-kg child (0.5 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The developmental toxicity study in rabbits by Miller (1983) has been selected as the basis for determination of the Ten-day HA value for propachlor. Pregnant rabbits administered propachlor (96.5%) by gavage at a dose level of 5 mg/kg/day showed no clinical signs of toxicity in the adult animals and no reproductive or developmental effects in the fetuses. The study identified a NOAEL of 5 mg/kg/day. These results are contrasted by a developmental study reported by Schardein et al. (1982) in which rats were administered doses ranging from 20 to 200 mg/kg/day during gestation, with no adverse fetotoxic or maternal effects reported at any dose level. The NOAEL identified in that study was 200 mg/kg/day (the highest dose tested). Since the rabbit appears to be the more sensitive species, the NOAEL identified in the rabbit study will be used to derive the Ten-day HA.

Using a NOAEL of 5 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(5\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.5\ \text{mg/L}\ (500\ \text{ug/L})$$

where:

5 mg/kg/day = NOAEL, based on the absence of clinical signs of toxicity and the lack of reproductive or teratogenic effects in rabbits exposed to propachlor by gavage for 12 days during gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

While there are two 90-day studies suitable for developing a longer-term HA, it was decided that it would be more appropriate to use the Reference Dose of 0.013 mg/kg/day and adjusting this number to protect a 10-kg child and a 70-kg adult since acute data indicate toxicological concern at low levels (Miller, 1983). The resulting Longer-term HA thus becomes 0.1 mg/L and 0.5 mg/L for a 10-kg child and a 70-kg adult, respectively.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

While there are no suitable studies to calculate a Lifetime HA, the 90-day study by Wazeter et al. (1964) has been selected to serve as the basis for determination of the Lifetime HA value for propachlor since it is the only data available of extended duration. Based on body and liver weight effects, a NOAEL of 13.3 mg/kg/day was identified. These results were further verified by the results of a similar study with rats conducted by Reyna et al. (1984a) in which a NOAEL of 12 mg/kg/day was identified.

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(13.3 \text{ mg/kg/day})}{(1{,}000)} = 0.013 \text{ mg/kg/day} \quad (10 \text{ ug/kg/day})$$

where:

13.3 mg/kg/day = NOAEL based on the absence of effects on body weight and liver weight in rats exposed to propachlor for 90 days.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Level (DWEL)

$$\text{DWEL} = \frac{(0.013 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.46 \text{ mg/L} \ (500 \text{ ug/L})$$

where:

0.013 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.46 mg/L) (20%) = 0.092 mg/L (90 ug/L)

where:

0.46 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No studies on the carcinogenic potential of propachlor were found in the available literature. However, other structurally similar compounds such as alachlor and acetochlor have been found to be probable carcinogens.

- Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), propachlor may be classified in Group D: not classified. This category is for substances with inadequate human and animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Residue tolerances ranging from 0.02 to 10.0 ppm have been established for propachlor in or on agricultural commodities (U.S. EPA, 1985).

- NAS (1977) has recommended an ADI of 0.1 mg/kg/day and a Suggested-No-Adverse-Effect Level (SNARL) of 0.7 mg/L, based on a NOAEL of 100 mg/kg/day in a rat study (duration of study not available).

VII. ANALYTICAL METHODS

- Analysis of propachlor is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using an electron capture detector. This method has been validated in a single laboratory, and the estimated detection limit for analytes such as propachlor is 0.5 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No data were found for the removal of propachlor from drinking water by conventional treatment or by activated carbon treatment.

- No data were found for the removal of propachlor from drinking water by aeration. However, the Henry's Coefficient can be estimated from available data on solubility (700 mg/L at 20°C) and vapor pressure (7.9×10^{-5} mm Hg at 25°C). Propachlor probably would not be amenable to aeration or air stripping because its Henry's Coefficient is approximately 3.8×10^{-9} m^3 atm. mol^{-1}. Baker and Johnson (1984) reported the results of water and pesticide volatilization from a waste disposal pit. Over a 2-year period, approximately 66.4 mg of propachlor evaporated for every liter of water which evaporated and only 8.3% of the propachlor was removed. These results support the assumption that aeration would not effectively remove propachlor from drinking water.

- Propachlor is similar in structure to alachlor and has similar physical properties. The effectiveness of various processes for removing propachlor would probably be similar to that of alachlor.

- Alachlor is amenable to the following processes:

  - GAC (Miltner and Fronk, 1985; DeFilippi et al., 1980).

  - PAC (Miltner and Fronk, 1985; Baker, 1983).

  - Ozonation (Miltner and Fronk, 1985).

  - Reverse osmosis (Miltner and Fronk, 1985).

- Chlorine and chlorine dioxide oxidation were partially effective in removing alachlor from drinking water (Miltner and Fronk, 1985).

- The following processes were not effective in removing alachlor from drinking water:

  - Diffused aeration (Miltner and Fronk, 1985).

  - Potassium permanganate oxidation (Miltner and Fronk, 1985).

  - Hydrogen peroxide oxidation (Miltner and Fronk, 1985).

  - Conventional treatment (Miltner and Fronk, 1985; Baker, 1983).

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*Confidential Business Information submitted to the Office of Pesticide Programs

August, 1988

PROPAZINE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

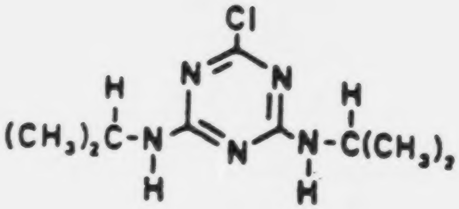
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 139-40-2

Structural Formula



6-Chloro-N,N'-bis(1-methylethyl)-1-3,5-triazine-2,4-diamine

Synonyms

- Geigy 30,028; Gesomil; Milogard; Plantulin; Primatol P; Propasin; Prozinex (Meister, 1983).

Uses

- Selective preemergence and preplant herbicide used for the control of most annual broadleaf weeds and annual grasses in milo and sweet sorghum (Meister, 1983).

Properties (Meister, 1983; IPC, 1984; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_9H_{16}N_5Cl$
Molecular Weight	230.09
Physical State (25°C)	Colorless crystals
Boiling Point	--
Melting Point	212 to 214°C
Density	--
Vapor Pressure (20°C)	2.9×10^{-8} mm Hg
Water Solubility (29°C)	8.6 mg/L
Octanol/Water Partition Coefficient	-1.21
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Propazine has been found in 33 of 1,097 surface water samples analyzed and in 15 of 906 ground water samples (STORET, 1988). Samples were collected at 244 surface water locations and 607 ground water locations. The 85th percentile of all non-zero samples was 2.3 ug/L in surface water and 0.2 ug/L in ground water sources. The maximum concentration found was 13 ug/L in surface water and 300 ug/L in ground water. Propazine was found in five States in surface water and in four States in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

° Propazine was detected in ground water in California at trace levels (<0.1 ppb) (U.S.G.S., 1985).

Environmental Fate

The following data were submitted by Ciba-Geigy and reviewed by the Agency (U.S. EPA, 1987):

° Hydrolysis studies show propazine to be resistant to hydrolysis. After 28 days, at pH 5, 60% remains; at pH 7, 92% remains; and at pH 9, 100% remains. Hydroxypropazine (2-hydroxy-4,6-bis-isopropylamino)-s-triazine) is the hydrolysis product.

° Propazine at 2.5 ppm in aqueous solution was exposed to natural sunlight for 17 days. In that time, 5% degraded to hydroxy-propazine.

° Under aerobic conditions, 10 ppm propazine was applied to a loamy sand (German) soil with 2.2% organic carbon. The soil was incubated at 25°C in the dark and kept at 70% of field capacity. Propazine degraded with a half-life of 15 weeks. Hydroxypropazine was the major degradate from aerobic soil metabolism; its concentration increased from 14% at 12 weeks to a maximum of 31% after 52 weeks of incubation. Trapped volatiles identified as CO_2 accounted for 1% of the applied propazine after 52 weeks. Bound residues increased up to 35% after 12 weeks of incubation.

° Under anaerobic conditions, further degradation of propazine was slight.

° Freundlich soil-water partition coefficient (Kd) values for propazine and hydroxypropazine were determined for four soils: a sand loam (0.7% OM), a sand loam (1.4% OM), a loam soil (2.9% OM) and a clay loam (8.3% OM). The Kd values were: 0.34, 1.13, 2.69 and 3.19, respectively, for propazine. On the same four soils the Kd values for hydroxypropazine were: 1.13, 2.94, 31.8 and 10.6, respectively. All Kd values have units of ml/gm.

° Leaching studies for propazine performed on four soils under worst-case conditions (30-cm columns leached with 20 inches of water) for propazine indicate propazine's mobility in soil-water systems. In a loamy sand (0.7% OM), a sandy loam (1.4% OM), a loam (1.7% OM), and a silt loam (2.4% OM), 82.5%, 18%, 69.5%, and 23.6% leached, respectively.

° In column studies using aged propazine, degradation products leached from a loamy sand soil with 2.2% OM. About 25% of the aged propazine added to the columns leached. In a loam soil with 3.6% OM, <0.05% of the aged propazine added to the columns leached.

- In field dissipation studies, propazine was found at 18 inches the deepest depth in the soil sampled. Hydroxypropazine was found at all depths and sites up to 3 years after application. Field half-lives for propazine were 5 to 33 weeks in the 0- to 6-inch depth, and 17 to 51 weeks at the 6 to 12 inch depth.

III. PHARMACOKINETICS

Absorption

- Bakke et al. (1967) administered single oral doses of ring-labeled ^{14}C-propazine to Sprague-Dawley rats. After 72 hours, about 23% of the label was recovered in the feces and about 66% was excreted in the urine. This indicates that gastrointestinal absorption was at least 77% complete.

Distribution

- Bakke et al. (1967) administered ring-labeled ^{14}C-propazine (41 to 56 mg/kg) to rats by gastric intubation. Radioactivity in a variety of tissues was observed to decrease from an average of 46.7 ppm 2 days posttreatment to 22.3 ppm after 8 days. Radioactivity was detected in the lung (30 ppm), spleen (25 ppm) heart (27 ppm), kidney (17 ppm) and brain (13 ppm) for up to 8 days. After 12 days, the only detectable quantities were in hide and hair (3.35% of administered dose), viscera (0.1%) and carcass (2.22%).

Metabolism

- Eighteen metabolites of propazine have been identified in the urine of rats given single oral doses of ^{14}C-propazine (Bakke et al., 1967). No other details were provided. Based on metabolites found in urine, Bakke et al. (1967) reported that dealkylation is one reaction in the metabolism of propazine. No other details were provided.

Excretion

- Bakke et al. (1967) administered single oral doses of ^{14}C-ring-labeled propazine to rats. Most of the radioactivity was excreted in the urine (65.8%) and feces (23%) within 72 hours. Excretion of propazine and/or metabolites was most rapid during the first 24 hours after administration, decreasing to smaller amounts at 72 hours.

IV. HEALTH EFFECTS

Humans

- Contact dermatitis was reported in workers involved in propazine manufacturing (Hayes, 1982). No other information on the health effects of propazine in humans was found in the available literature.

Animals

Short-term Exposure

- The reported acute oral LD_{50} values for propazine (purity not specified) were >5,000 mg/kg in mice (Stenger and Kindler, 1963b) and 1,200 mg/kg in guinea pigs (NIOSH, 1987).

- Stenger and Kindler (1963a) reported that dietary administration of propazine (purity not specified) to rats (five/sex/dose) at doses of 1,250 or 2,500 mg/kg for 4 weeks resulted in a decrease in body weight, but there were no pathological alterations in organs or tissues. No other details were provided.

Dermal/Ocular Effects

- The acute dermal LD_{50} value in rabbits for propazine (90% water dispersible granules) was reported as >2,000 mg/kg (Cannelongo et al., 1979).

- Stenger and Huber (1961) reported that rats were unaffected when a 5% gum arabic suspension of propazine (0.4 mL/animal) was applied once a day for 5 consecutive days to shaved and intact skin of five rats then washed away 3 hours after application.

- Palazzolo (1964) reported that propazine (1 or 2 g/kg/day) applied to intact or abraded skin of albino rabbits (five/sex/dose) for 7 hours produced mild erythema, drying, desquamation and thickening of the skin. Body weights, mortality, behavior, hematology, clinical chemistry and pathology of the treated and untreated groups were similar.

Long-term Exposure

- In 90-day feeding studies by Wazeter et al. (1967a), beagle dogs (12/sex/dose) were fed propazine (80 WP) in the diet at 0, 50, 200 or 1,000 ppm active ingredient. Based on the assumption that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959) these doses correspond to 0, 1.25, 5.0 or 25 mg/kg/day. No compound-related changes were observed in general appearance, behavior, hematology, urinalysis, clinical chemistry, gross pathology or histopathology at any dose tested. In the 1,000 ppm dose group, four dogs lost 0.3 to 1.1 kg in body weight, which the author suggested may have been compound-related (no p value reported). Based on these results, a No-Observed-Adverse-Effect Level (NOAEL) of 200 ppm (5 mg/kg/day) and a LOAEL of 1,000 ppm (25 mg/kg/day) were identified.

- Wazeter et al. (1967b) supplied CD rats (80/sex/dose) with propazine (80 WP) in the diet for 90 days at dose levels of 0, 50, 200 or 1,000 ppm active ingredient. Based on the assumption that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to 0, 2.5, 10 or 50 mg/kg/day. No compound-related changes were observed in appearance, general behavior, hematology, clinical chemistry, urinalysis, gross pathology and histopathology. There was a 12% reduction ($p < 0.01$) in body weight of females at 1,000 ppm (50 mg/kg/day) at the end of the study. Based on body weight loss, a NOAEL of 200 ppm (10 mg/kg/day) and a Lowest-Observed-Adverse-Effect Level (LOAEL) of 1,000 ppm (50 mg/kg/day) were identified.

- Geigy (1960) dosed rats (12/sex/dose) of an unspecified strain with propazine (50% a.i.) by stomach tube for 90 days at 0, 250 or 2,500 mg/kg/day (a.i.) or for 180 days at 0 or 250 mg/kg/day (a.i.). In the 90-day study, a reduction in body weight and feed consumption were reported at 2,500 mg/kg/day, but no effects were seen at 250 mg/kg/day. No histopathological evaluations were performed at the high-dose level. After 180 days, rats administered propazine at 250 mg/kg/day were similar to untreated controls in growth rates, daily food consumption, gross appearance and behavior, mortality, gross pathology and histopathology. This study identified a NOAEL of 250 mg/kg/day and a LOAEL of 2,500 mg/kg/day.

- Jessup et al. (1980a) fed CD mice (60/sex/dose) technical propazine (purity not specified) for 2 years at dose levels of 0, 3, 1,000 or 3,000 ppm. Based on the assumption that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these doses correspond to 0, 0.45, 150 or 450 mg/kg/day. The general appearance, behavior, survival rate, body weights, organ weights, food consumption and incidence of inflammatory, degenerative or proliferative alterations in various tissues and organs did not differ significantly from untreated controls. The author identified a NOAEL of 3,000 ppm (450 mg/kg/day, the highest dose tested).

- Jessup et al. (1980b) fed CD rats (60 to 70/sex/dose) technical propazine (purity not specified) in the diet for 2 years at dose levels of 0, 3, 100 or 1,000 ppm. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.15, 5 or 50 mg/kg/day. No compound-related effects were observed in behavior, appearance, survival, feed consumption, hematology, urinalysis and in nonneoplastic alterations in various tissues and organs. Mean body weight gains appeared to be lower in the treatment groups than the control groups. Body weights at 104 weeks were lower than controls at all dose levels. The percent decreases in males and females were as follows: -6.3 and -3.9% (3 ppm); -4.6 and -5.6% (100 ppm); -13.1 and -11.4% (1,000 ppm). These decreases were statistically significant in males at 3 and 1,000 ppm, and in females at 100 and 1,000 ppm. The decreases at 3 or 100 ppm appeared to be so small that they may not be considered biologically significant; a NOAEL was identified at 100 ppm (5 mg/kg/day).

Reproductive Effects

- Jessup et al. (1979) conducted a three-generation study in which CD rats (20 females and 10 males/dose) were administered technical propazine in the diet at 0, 3, 100 or 1,000 ppm. Based on the assumption that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.15, 5 or 50 mg/kg/day. No compound-related effects were observed in any dose group in general behavior, appearance or survival of parental rats or pups. The mean parental body weights were statistically lower at 1,000 ppm (50 mg/kg/day). No differences were reported in feed consumption for treated and control animals. No treatment-related effects were observed in fertility, length of gestation or viability and surivival of the pups through weaning. Mean pup weights at lactation were not adversely affected at 3 or 100 ppm (0.15 or 5 mg/kg/day). However, at 1,000 ppm (50 mg/kg/day), there was a statistically significant decrease in mean pup weights for all generations except F_{1a}. Based on these data, a NOAEL of 100 ppm (5 mg/kg/day) was identified.

Developmental Effects

- Fritz (1976) administered technical propazine (0, 30, 100, 300 or 600 mg/kg/bw) orally by intubation to pregnant Sprague-Dawley rats (25/dose) on days 6 through 15 of gestation. No maternal toxicity, fetotoxicity or teratogenic effects were observed at 100 mg/kg/day or lower. Maternal body weight and feed consumption were reduced at 300 mg/kg/day or higher. Fetal body weight was reduced, and there was delayed skeletal ossification (of calcanei) at 300 mg/kg/day or higher. Based on body weights, a maternal NOAEL of 100 mg/kg/day and a fetal NOAEL of 100 mg/kg/day were identified.

- Salamon (1985) dosed pregnant CD rats (21 to 23 animals per dose group) with technical propazine (99.1% pure) by gavage at dose levels of 0, 10, 100 or 500 mg/kg/day on days 6 through 15 of gestation. Maternal body weight and feed consumption were statistically significantly ($p < 0.05$) decreased at doses of 100 mg/kg/day or higher. Fetal body weight was reduced, and ossification of cranial structures was delayed at 500 mg/kg/day. Based on maternal toxicity, a NOAEL of 100 mg/kg/day was identified.

Mutagenicity

- Puri (1984a) reported that propazine (0, 0.4, 20, 100 or 500 ug/mL) did not produce DNA damage in human fibroblasts *in vitro*.

- Puri (1984b) reported that propazine (0, 0.50, 2.5, 12.5 or 62.5 ug/mL) did not cause DNA damage in rat hepatocytes *in vitro*.

- Strasser (1984) reported that propazine administered to Chinese hamsters by gavage (0, 1,250, 2,500 or 5,000 mg/kg) did not cause anomalies in nuclei of somatic interphase cells.

Carcinogenicity

- Innes et al. (1969) fed propazine in the diet to 72 mice (C57BL/6 x AKR)F_1 or (C57BL/6 x C3H/ANf)F_1 for 18 months at a dose level of 0 or 46.4 mg/kg/day. Based on histopathological examination of tissues (no data reported), the authors stated that propazine, at the one dose tested, did not cause a statistically significant increase in the frequency of any tumor type in any sex-strain subgroup or combination of groups.

- Jessup et al. (1980b) fed CD rats (60 to 70/sex/dose) technical propazine (purity not specified) in the diet for 2 years at dose levels of 0, 3, 100 or 1,000 ppm. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.15, 5 or 50 mg/kg/day. Tumor incidence was evaluated for a variety of organs and tissues. The most commonly occurring tumors were mammary gland tumors in female rats. At the highest dose tested (1,000 ppm, 50 mg/kg/day), the authors reported an increase in adenomas (10/55, 18%), adenocarcinomas (9/55, 16%) and papillary carcinomas (8/55, 15%) compared to corresponding tumor levels in untreated controls (3/55, 5%), (6/55, 11%) and (4/55, 7%), respectively. Also, it was reported that the percentage of tumor-bearing rats was 73% in the high-dose treated group compared to 50% in corresponding untreated controls. The authors did not consider these increases to be statistically significant. However, in 1981, Somers reported historical control values of 122/1,248 (10%) for adenomas and of 769/1,528 (50%) for percentage of tumor-bearing animals. Further evaluations by Somers (1981) of the above data (control and treated) and historical control data indicated that the increase in mammary gland adenomas and the number of rats bearing one or more tumor was statistically significant ($p < 0.02$).

- Jessup et al. (1980a) fed CD mice (60/sex/dose) technical propazine (purity not stated) for 2 years at dose levels of 0, 3, 1,000 or 3,000 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.45, 150 or 450 mg/kg/day. The incidence of proliferative and neoplastic alterations in the treated groups did not differ significantly from the control group at any dose level.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for propazine. It is, therefore, recommended that the Ten-day HA value for a 10-kg child, 1.0 mg/L (1,000 ug/L, calculated below), be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Salamon (1985) has been selected to serve as the basis for the determination of Ten-day HA value for propazine. In this teratogenicity study in rats, body weight was decreased in dams dosed on days 6 to 15 of gestation with 100 mg/kg/day or greater. No adverse effects were observed in either dams or fetuses at 100 mg/kg/day. The rat study by Fritz (1976) reported maternal and fetal toxicity at 300 mg/kg/day, but not at 100 mg/kg/day. This NOAEL was not selected, since maternal weight loss was noted at this dose by Salamon (1985).

Using a NOAEL of 10 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(10\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 1.0\ \text{mg/L}\ (1{,}000\ \text{ug/L})$$

where:

10 mg/kg/day = NOAEL, based on absence of maternal and developmental toxicity in rats exposed to propazine by gavage on days 6 through 15 of gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The 90-day feeding study in dogs by Wazeter et al. (1967a) has been selected to serve as the basis for the Longer-term HA for propazine. In this study, body weight loss occurred at 1,000 ppm (25 mg/kg). A NOAEL of 200 ppm (5 mg/kg/day) was identified. This is supported by the 90-day rat feeding study by Wazeter et al. (1967b), which identified a NOAEL of 10 mg/kg/day and a LOAEL of 50 mg/kg/day. The 90-day study in rats by Geigy (1960) has not been selected, since the NOAEL (250 mg/kg/day) is higher than the LOAEL values reported above.

Using a NOAEL of 5 mg/kg/day, the Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(5\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.5\ \text{mg/L}\ (500\ \text{ug/L})$$

where:

5 mg/kg/day = NOAEL, based on absence of effects on appearance, behavior, hematology, urinalysis, clinical chemistry, gross pathology, histopathology and body weight gain in dogs exposed to propazine via the diet for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(5\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 1.75\ \text{mg/L}\ (2{,}000\ \text{ug/L})$$

where:

5 mg/kg/day = NOAEL, based on absence of effects on appearance, behavior, hematology, urinalysis, clinical chemistry, gross pathology, histopathology and body weight gain in dogs exposed to propazine via the diet for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classifed as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in rats by Jessup et al. (1980b) has been selected to serve as the basis for determination of the Lifetime HA for propazine. No effects were detected on behavior, appearance, mortality, food consumption, hematology, urinalysis or body weight gain at doses of 5 mg/kg/day. At 50 mg/kg/day, decreased weight gain was noted, and there was evidence of increased tumor frequency in the mammary gland. This NOAEL value (5 mg/kg/day) is supported by the NOAEL of 5 mg/kg/day in the three-generation reproduction study in rats by Jessup et al. (1979). The 2-year feeding study in mice by Jessup et al. (1980a) has not been selected, since the data suggest that the mouse is less sensitive than the rat.

The Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(5\ \text{mg/kg/day})}{(100)\ (3)} = 0.02\ \text{mg/kg/day}$$

where:

5 mg/kg/day = NOAEL, based on absence of effects on behavior, appearance, mortality, hematology, urinalysis or body weight gain in rats exposed to propazine via the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = additional uncertainity factor to account for data gaps (chronic feeding dog study) in the propazine database.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.02\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.70\ \text{mg/L}\ (700\ \text{ug/L})$$

where:

0.02 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(0.70 \text{ mg/L})\ (20\%)}{(10)} = 0.014 \text{ mg/L } (10 \text{ ug/L})$$

where:

0.70 mg/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- No evidence of increased tumor frequency was detected in a 2-year feeding study in mice at doses up to 450 mg/kg/day (Jessup et al., 1980a) or in an 18-month feeding study in mice at a dose of 46.4 mg/kg/day (Innes et al., 1969).
- Jessup et al. (1980b) reported that the occurrence of mammary gland tumors in female rats administered technical propazine in the diet for 2 years at 1,000 ppm (50 mg/kg/day) was increased but did not differ significantly from concurrent controls. However, a reevaluation of the data by Somers (1981) that considered historical control data indicated that the increase in mammary gland adenomas and the number of rats bearing one or more tumors was statistically significant ($p < 0.02$).
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of propazine.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), propazine may be classified in Group C: possible human carcinogen. This category is for substances with limited evidence of carcinogenicity in animals in the absence of human data.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA (1986b) has established residue tolerances of 0.25 ppm for propazine in or on various agricultural commodities (negligible) based on a Provisionary Acceptable Daily Intake (PADI) of 0.005 mg/kg/day.
- NAS (1977) determined an Acceptable Daily Intake (ADI) of 0.464 mg/kg/day, based on a NOAEL of 46.4 mg/kg identified in an 80-week feeding study in mice with an uncertainty factor of 1,000.
- NAS (1977) calculated a chronic Suggested-No-Adverse-Effect-Level (SNARL) of 0.32 mg/L, based on an ADI of 0.0464 mg/kg/day and a relative source contribution factor of 20%.

VII. ANALYTICAL METHODS

- Analysis of propazine is by a gas chromatographic (GC) using method #507, a method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen-phosphorus detector. This method has been validated in a single laboratory and the limit of detection for propazine was 0.13 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information regarding treatment technologies applicable to the removal of propazine from contaminated water was found in the available literature.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

PROPHAM

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

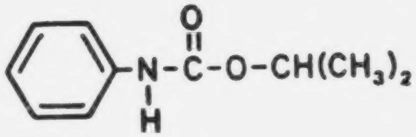
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 122-42-9

Structural Formula



Phenyl 1-methylethyl carbamate; isopropyl-N-phenylcarbamate; Isoproopyl carbanilate.

Synonyms

- IPC, IFC, Ban-Hoe, Beet-Kleen, Chem-Hoe, Premalox, Triherbide-IPC, Tuberite (Meister, 1988).

Uses

- Pre- and postemergence herbicide for control of weeds in alfalfa, clover, flax, lettuce, safflower, spinach, sugarbeets, lentils and peas and on fallow land. Prevents cell division. Acts on meristematic tissue (Meister, 1988).

Properties (Meister, 1988; Cohen, 1984; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_{10}H_{13}O_2N$
Molecular Weight	179.21
Physical State (25°C)	White crystals
Boiling Point (at 25 mm Hg)	--
Melting Point	87°C
Density	1.09 g/mL (20°C)
Vapor Pressure (25°C)	(sublimes slowly at 25°C)
Specific Gravity (20°C/20°C)	1.09
Water Solubility (25°C)	250 mg/L
Log Octanol/Water Partition Coefficient	1.22 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Propham has been found in 1 of 392 surface water samples analyzed and was undetectable in 583 ground water samples (STORET, 1988). Samples were collected at 131 surface water locations and 572 ground water locations, and propham was found in Texas. The 85th percentile of the sample and the maximum concentration found in surface water was 2 ug/L. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Ring-labeled ^{14}C-propham (purity unspecified), at 4 ppm in unbuffered distilled water declined to 2.4 ppm during 14 days of irradiation with a Pyrex-filtered light (uncharacterized) at 25°C (Gusik, 1976). Degradation products included isopropyl 4-hydroxycarbanilate (3.5% of applied propham), isopropyl 4-aminobenzoate (approximately 0.1%), 1-hydroxy-2-propylcarbanilate (approximately 0.1%), and polymeric materials (10 to 12%). No degradation occurred in the dark control during the same period.

- Under aerobic conditions, ring-labeled ^{14}C-propham (test substance uncharacterized), at 2 ppm, degraded with a half-life of 2 to 7 days in silt loam soil, (Hardies, 1979; Hardies and Studer, 1979a), 4 to 7 days in loam soil (Hardies and Studer, 1979b), and 7 to 14 days in sandy loam soil (Hardies and Studer, 1979c) when incubated in the dark at approximately 25°C and 60% of water holding capacity.

- Under anaerobic conditions, ring-labeled ^{14}C-propham (test substance uncharacterized) declined from 8.5 to <5% of the applied radioactivity during 60 days of incubation in silt loam soil in the dark at approximately 25°C and 60% of water holding capacity (Hardies 1979; Hardies and Studer, 1979a). Under anaerobic conditions, ring-labeled ^{14}C-propham (test substance uncharacterized) declined from approximately 0.08 to approximately 0.04 ppm during 61 days of incubation in loam soil in the dark at approximately 25°C and 60% of water holding capacity (Hardies and Studer, 1979b); in sandy loam soil, the decline was from approximately 0.06 to 0.03 ppm during 63 days of incubation (Hardies and Studer, 1979c).

- ^{14}C-Propham (purity unspecified) at 0.2 to 20 ppm was adsorbed to two silt loams, a silty clay loam, a sandy clay loam, and two sandy loam soils with Freundlich K values of 0.74 and 2.72, 1.77, 0.65, and 0.27 and 1.58, respectively (Hardies and Studer, 1979d). Ring-labeled ^{14}C-propham (purity unspecified) was very mobile (>98% of applied propham in leachate) in 30.5-cm columns of sandy clay loam and sandy loam soil leached with 20 inches of water (Hardies and Studer, 1979e). It was less mobile in columns of Babcock silt loam (42.3% in leachate), silty clay loam (approximately 62% at 11- to 27-cm depth), and Wooster silt loam (approximately 54% at 7.6- to 15-cm depth) soils. Aged (30-day) residues were relatively immobile in Wooster silt loam soil; <1% of the applied radioactivity moved from the treated soil.

- Propham residues dissipated from the upper 6 inches of sandy loam, sandy clay loam, silty loam, and silty clay loam field plots with half-lives of 42 to 94, 57 to 160, 42 to 147, and approximately

21 to 42 days, respectively, following application of propham (ChemHoe 135, 3 lb/gal F1C) at 4 and 8 lb active ingredient (a.i.) per acre in September-November, 1977 (Pensyl and Wiedmann, 1979). Residues were nondetectable (<0.02 ppm) within 164 to 283 days after treatment at all rates and sites. In general, propham residues in the 6- to 12-inch depth were <0.04 ppm. Propham (3 lb/gal F1C) applied at 6 lb a.i./A in mid-May dissipated with a half-life of 10 to 15 days in the 0- to 6-inch depth of silt loam soil (Wiedmann and Pensyl, 1981). Ring-labeled ^{14}C-propham (formulated as ChemHoe 135) applied at 4 lb a.i./A dissipated with a half-life of <7 days in the upper 3 inches of silt loam soil treated in November, 1981 (Wiedmann et al., 1982). The second half-life occurred approximately 133 days post-treatment.

III. PHARMACOKINETICS

Absorption

- After oral administration of 1,100 mg/kg ^{14}C-isopropyl-labeled propham (99% a.i.) to rats (1,100 mg/kg), 88% of the label appeared in urine within 4 days. After oral doses of 1,100 mg/kg of ^{14}C-phenyl-labeled propham, 96% was excreted in urine and 2% was excreted in feces (Chen, 1979).

- Fang et al. (1972) reported that in rats given oral doses (ranging from less than 4 mg/kg to 200 mg/kg) of ^{14}C-propham (99% a.i.) 80 to 85% was excreted in urine and 5% was expired in air, indicating that propham is well absorbed (85 to 98%) from the gastrointestinal tract.

Distribution

- Chen (1979) administered single oral doses of ^{14}C-phenyl- or ^{14}C-isopropyl-labeled propham (1,100 mg/kg 99% a.i.) to rats. Trace amounts of both ^{14}C-phenyl- or ^{14}C-isopropyl-labeled (0.5 to 1.2%) propham were present in the liver, kidneys, muscle and carcass after 48 hours.

- Paulson and Jacobsen (1974) administered single oral doses of ^{14}C-propham (100 mg/kg 99% a.i.) to goats. Six hours later, only low levels (0.2%) were detectable in milk.

Metabolism

- Chen (1979) administered single oral doses of ^{14}C-phenyl-labeled propham (1,100 mg/kg 99% a.i.) to rats by gavage. Most of the dose (96%) was excreted in urine as metabolites. The primary metabolites identified were the sulfate ester conjugate and the glucuronide conjugate of isopropyl 4-hydroxycarbanilate, which accounted for 78 and 1.3%, respectively, of the total primary metabolites recovered. Similar studies in rats (single oral dose of 100 mg/kg) by Paulson et al. (1972) support the rapid metabolism and excretion of propham. In these studies a third metabolite (the sulfate ester of 4-hydroxy-acetanilide) and a fourth (unidentified) metabolite were found to account for 12.3% and 8.9%, respectively, of the total metabolites detected in urine. The data demonstrate that ring hydroxylation at the 4-position and subsequent conjugation as well as hydrolysis and subsequent N-acetylation occurred prior to excretion.

Excretion

- ^{14}C-Propham is rapidly excreted primarily in the urine of rats. Peak urinary concentrations were reached 6 hours post-treatment. It was found that 96% and 2% of the administered dose of ^{14}C-propham (100 mg/kg; 99% a.i.) was excreted in the urine and feces, respectively (Chen, 1979; Paulson et al., 1972).
- Fang et al. (1972) reported that after oral administration of ring- or chain-^{14}C-labeled propham (99% a.i.) to rats, 80 to 85% of the administered dose was excreted in the urine over a 3-day period. In animals dosed with ^{14}C-isopropyl-labeled propham, 5% was detected as expired carbon dioxide.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of propham in humans.

Animals

Short-term Exposure

- Terrell and Parke (1977) administered single oral doses of propham (technical grade, purity not specified) to groups of 10 male and 10 female rats and monitored adverse effects for 14 days. Doses of 2,000 mg/kg produced loss of righting reflex, ptosis, piloerection, decreased locomotor activity, chronic pulmonary disease and rugae and irregular thickening of the stomach. The acute oral LD_{50} values in male and female rats were reported to be 3,000 ± 232 mg/kg and 2,360 ± 118 mg/kg, respectively. A No-Observed-Adverse-Effect Level (NOAEL) cannot be derived from the study because the doses used were too high, and adverse effects were found at all doses tested.
- Brown and Gross (1949) reported that when a single dose of 1,136 mg/kg propham (purity not specified) was administered orally to 8 Sprague-Dawley rats, no adverse effects were observed. A dose of 2,174 mg/kg resulted in periods of light anesthesia, a higher dose of 3348 mg/kg resulted in light anesthesia and death (one death in 6 tested). Deep anesthesia was produced when 4,425 mg/kg of propham was administered to rats with subsequent death of 38% of the test animals (3 deaths in 8 animals tested).
- The acute inhalation LC_{50} value in albino rats was reported to be 10.71 mg/L (or 10,710 mg/m^3, PPG Industries, 1978).

Dermal/Ocular Effects

- The acute dermal LD_{50} value in albino rabbits was reported to be greater than 3,000 mg/kg (PPG Industries, 1978).

- Propham (3% aqueous solution) was slightly irritating when applied to the skin and eyes of albino rabbits (PPG Industries, 1978).

Long-term Exposure

- Tisdel et al. (1979) fed Sprague-Dawley rats (30/sex/dose) propham (technical grade, purity not specified) in the diet at 0, 250, 1,000 or 2,000 ppm for 91 days. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels are equivalent to 0, 12.5, 50 or 100 mg/kg/day. Following treatment, body weight, organ weight, growth, clinical chemistry, gross pathology and histopathology were evaluated. No effects were reported at 1,000 ppm (50 mg/kg/day) or lower in any parameters measured. At the highest dose (2,000 ppm or 100 mg/kg/day) there was a significant increase in spleen weight ($p < 0.05$) and in spleen-to-body weight ratio ($p < 0.01$) in males, and a 70% inhibition of plasma cholinesterase ($p < 0.01$) in females at 45 days. Based on the above data, a NOAEL of 1,000 ppm (50 mg/kg/day) was identified.

Reproductive Effects

- In a report of a three-generation rat reproduction study, Ravert (1978) reported data from the P_2 to weaning of the F_{2b} generation. Sprague-Dawley rats (10 males or 20 females/dose) were administered technical grade propham (purity not specified) in the diet at dose levels of 0, 87.5, 250, 750 or 1,500 ppm for 9 weeks prior to breeding for each parental generation. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels are equivalent to 0, 4.4, 12.5, 37.5 or 75 mg/kg/day. It was not clear whether the test animals were also fed propham-containing diets during pregnancies or through weaning of offspring. No effects were reported on fertility, mortality or pup development at any dose level tested.

Developmental Effects

- Ravert and Parke (1977) administered technical propham (purity not specified) by gavage to pregnant Sprague-Dawley rats (16 to 20/dose), at levels of 0, 37.6, 376 or 1,879 mg/kg/day on days 6 through 15 of gestation. End points that were monitored included maternal and fetal body weight and the number of corpora lutea, implants, live fetuses and dead fetuses. Fetuses were also examined for soft-tissue and skeletal anomalies. The only effects detected were reduced maternal and fetal body weights and higher resorption rates at the highest dose tested (1,879 mg/kg) and increased incidences of incomplete ossification of the parietal and frontal bones of the skull at 375.8 and 1,879 mg/kg. An apparent NOAEL appears to be 37.6 mg/kg/day.

However, in this experiment, the high dose (1,879 mg/kg/day is too high (i.e., one-half of the LD_{50}); nearly two-thirds of the pregnant rats at this dose died prior to scheduled sacrifice. Further, the dose intervals are also relatively large. Therefore, a reliable NOAEL can not be determined accurately due to the large difference in dosages tested and the marginal effect noted at 376 mg/kg/day (For more information on the developmental effects, see Worthing, 1979).

Mutagenicity

- Using the Ames *Salmonella* test, Margard (1978) reported that propham (purity not specified, 1,000 ug/plate) did not show any indications of mutagenic activity either with or without activation.

- When propham (100 ug/mL, purity not specified) was applied to cultures containing BALB/c 3T3 cell lines, no clonal transformation was evident (Margard, 1978).

- Friedrick and Nass (1983) reported that propham (1.1 to 2.2 mM) did not induce mutation in S49 mouse lymphoma cells.

Carcinogenicity

- Innes et al. (1969) administered propham to (C57BL/6 X C3H/ANf) or (C7BL/6 X AKR) mice (18/sex) in the diet at 0 or 560 ppm for 18 months. According to the author, this corresponds to a dose of about 0 to 215 mg/kg. The incidence of tumors was not significantly increased ($p > 0.05$) for any tumor type in any sex-strain subgroup or in the combined sexes of either strain. This duration of exposure and this dose level may not be sufficient for detecting late-occurring tumors.

- Hueper (1952) fed 15 Osborne-Mendel rats (sex not specified) dietary propham (20,000 ppm, purity not specified) for 18 months. The animals were alternately placed from 1 to 2 months on the diet followed by 1 to 2 weeks on normal diet. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), the dietary level was equivalent to 1,000 mg/kg/day. The time-weighted average can not be calculated due to a lack of detailed reporting of the study design. No tumors were observed in 6 of 8 surviving rats that were evaluated histologically. This study is limited by the low number of animals used, the poor survival rate, short duration, limited histopathological examination and method of treatment.

- Van Esch and Kroes (1972) fed groups of 23 to 26 golden hamsters 0 or 0.2% propham (2,000 ppm, purity not specified) in the diet for 33 months. Assuming that dietary assumptions appropriate for guinea pigs are also appropriate for hamsters and that 1 ppm in the diet of hamsters is equivalent to 0.04 mg/kg/day (Lehman, 1959), these levels are equivalent to 0 or 80 mg/kg/day. Based on histological examination, the authors reported no significant increase in tumor incidence.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L} \ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for propham. It is, therefore, recommended that the Longer-term HA value for a 10-kg child, 5 mg/L, calculated below, be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The Longer-term HA of 5 mg/L for a 10-kg child, calculated below, is used for the Ten-day HA since the apparent NOAEL (37.6 mg/kg/day) in the teratology study by Ravert and Parke (1977) was not necessarily the highest NOAEL, due to the large difference between the doses selected (a ten-fold difference between 37.6 and 376 mg/kg/day).

Longer-term Health Advisory

The study by Tisdel et al. (1979) has been selected to serve as the basis for the Longer-term HA value for propham. In this study, rats were fed propham in the diet for 91 days. At 100 mg/kg/day, plasma cholinesterase was inhibited (70%) and spleen-to-body weight ratios were increased. No effects were observed at 50 mg/kg/day. This NOAEL is supported by the NOAEL of 75 mg/kg/day identified in the three-generation reproduction study in rats by Ravert (1978).

Using a NOAEL of 50 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(50\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 5.0\ \text{mg/L}\ (5{,}000\ \text{ug/L})$$

where:

50 mg/kg/day = NOAEL, based on the absence of inhibition of cholinesterase or effects on organ weights in rats fed propham in the diet for 91 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(50\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 17.5\ \text{mg/L}\ (20{,}000\ \text{ug/L})$$

where:

50 mg/kg/day = NOAEL, based on the absence of inhibition of cholinesterase or effects on organ weights in rats fed propham in the diet for 91 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

No chronic study was found in the available literature that was suitable for determination of the Lifetime HA value for propham. The chronic studies by Innes et al. (1969), Hueper (1952) and Van Esch and Kroes (1972) did not provide adequate data on noncarcinogenic end points. In the absence of appropriate chronic data, the 91-day study by Tisdel et al. (1979), which identified a NOAEL of 50 mg/kg/day and was selected to serve as the basis for the Longer-term HA, has also been selected for deriving the Lifetime HA.

Using this study, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(50\ \text{mg/kg/day})}{(1{,}000)\ (3)} = 0.02\ \text{mg/kg/day (rounded from } 0.017\ \text{mg/kg/day)}$$

where:

50 mg/kg/day = NOAEL, based on the absence of any cholinesterase inhibition or effects on organ weights in rats fed propham in the diet for 91 days.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

3 = additional uncertainty factor. This factor is used to account for a lack of adequate chronic toxicity studies in the data base, preventing establishment of the most sensitive toxicological end point.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.017\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.595\ \text{mg/L}\ (600\ \text{ug/L})$$

where:

0.017 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.595\ \text{mg/L})\ (20\%) = 0.12\ \text{mg/L}\ (100\ \text{ug/L})$$

where:

0.595 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

° The International Agency for Research on Cancer (IARC, 1976) evaluated propham and concluded that the carcinogenic potential is currently cannot be determined.

° Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), propham may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

° No information on other existing criteria, guidelines and standards was found in the available literature.

VII. ANALYTICAL METHOD

° Analysis of propham is done by Method #4 of the NPS survey methods, "Determination of Pesticides in Groundwater by High Performance Liquid Chromatography with an Ultraviolet Detector" (U.S. EPA, 1986b). In this method a 1 liter sample is extracted with methylene chloride, reduced to 5 ml with methanol substitution and analysis by HPLC with a UV detector. The method is being validated in a single laboratory and the estimated detection limit for propham is 0.75 ug/L.

VIII. TREATMENT TECHNOLOGIES

° Available data indicate that granular activated carbon (GAC) adsorption will remove propham from water.

° Whittaker (1980) experimentally determined adsorption isotherms for propham on GAC.

° Whittaker (1980) reported the results of studies with GAC columns operating under bench scale conditions. At a flow rate of 0.8 gal/min/sq ft and an empty bed contact time of 6 minutes, propham breakthrough (when effluent concentration equals 10% of influent concentration) occurred after 720 bed volumes (BV).

° In the same study, Whittaker (1980) reported the results for seven propham bi-solute solutions when passed over the same GAC continuous-flow column.

- The studies cited above indicate that GAC adsorption is the most promising treatment technique for the removal of propham from water. However, selection of an individual technology or combinations of technologies for propham removal from water must be based on a case-by-case technical evaluation and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

SIMAZINE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

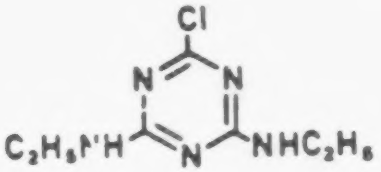
Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

The information used in preparing this Health Advisory was collected primarily from the open literature and the Simazine Registration Standard (U.S. EPA, 1983).

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 122-34-9

Structural Formula



2-Chloro-4,6-bis(ethylamino)-1,3,5-triazine

Synonyms

- Aquazine, Cekusan, Framed (discontinued by Farmoplant), G-27692, Gesatop, Primatol, Princep, Simadex, Simanex, Tanzene (Meister, 1984).

Uses

- Simazine is used as a selective preemergence herbicide for control of most annual grasses and broadleaf weeds in corn, alfalfa, established Bermuda grass, cherries, peaches, citrus, different kinds of berries, grapes, apples, pears, certain nuts, asparagus, certain ornamental and tree nursery stock, and in turf grass soil production (Meister, 1984). It is also used to inhibit the growth of most common forms of algae in aquariums, ornamental fish ponds and fountains. At higher rates, it is used for nonselective weed control in industrial areas.

Properties (Berg, 1984; Freed, 1976; Windholz et al., 1983; Reinert and Rogers, 1987)

Chemical Formula	$C_7H_{12}ClN_5$
Molecular Weight	201.69
Physical State (room temperature)	White, crystalline solid
Boiling Point	--
Melting Point	225 to 227°C
Density	1.302 g/cm^3
Vapor Pressure (20°)	6.1×10^{-9} mm Hg
Water Solubility (20°)	3.5 mg/L
Log Octanol/Water Partition Coefficient	2.51
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Simazine has been found in 922 of 5,873 surface water samples analyzed and in 202 of 2,654 ground water samples (STORET, 1988). Samples were collected at 620 surface water locations and 2,128 ground water locations. The 85th percentile of all non-zero samples was 2.18 ug/L in surface water and 1.60 ug/L in ground water sources. The maximum concentration found in surface water was 1,300 ug/L, and in ground water it was 800 ug/L. Simazine was found in surface water in 16 states and in ground water in 8 states. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Simazine has been found in ground water in California, Pennsylvania and Maryland; typical positives were 0.2 to 3.0 ppb (Cohen et al., 1986).

Environmental Fate

- Simazine did not hydrolyze in sterile aqueous solutions buffered at pH 5, 7 or 9 (20°C) over a 28-day test period (Gold et al., 1973).

- Under aerobic soil conditions, the degradation of simazine depends largely on soil moisture and temperature (Walker, 1976). In a sandy loam soil, half-lives ranged from 36 days to 234 days. Simazine applied to loamy sand and silt loam soils and incubated (25 to 30°C) for 48 weeks, dissipated with half-lives of 16.3 and 25.5 weeks, respectively (Monsanto Company, date not available). Simazine degradation products, 2-chloro-4-ethylamino-6-amino-s-triazine (G-28279), 2-chloro-4,6 bis(amino)-s-triazine, and several unidentified polar compounds were detected 32 and 70 days after a sandy loam soil had been treated with ^{14}C-simazine (Beynon et al., 1972). The degradates 2-hydroxy-4,6=bis(ethylamino)-s-triazine and 2-hydroxy-4-ethylamino-6-amino-s-triazine were also detected in aerobic soil (Keller, 1978).

- Under anaerobic conditions, ^{14}C-simazine had a half-life of 8 to 12 weeks in a loamy sand soil (Keller, 1978). The treated soil (10 ppm) was initially maintained for 1 month under aerobic conditions, followed by 8 weeks under anaerobic conditions (flooded with water and nitrogen). Degradates found included G-28279, 2-chloro-4,6-bis(amino)-s-triazine, 2-hydroxy-4,6-bis(ethylamino)-s-triazine, and 2-hydroxy-4-ethylamino-6-amino-s-triazine.

- Simazine is expected to be slightly to very mobile in soils ranging in texture from clay to sandy loam based on column leaching, soil thin-layer chromatography (TLC), and adsorption/desorption (batch equilibrium) studies. Using batch equilibrium tests, K_d values determined for 25 Missouri soils ranged from 1.0 for a sandy loam to 7.9 for a silty loam (Talbert and Fletchall, 1965). Simazine adsorption was correlated with soil organic matter content and, to a lesser extent, with cation exchange capacity (CEC) and clay content (Talbert and Fletchall, 1965; Helling and Turner, 1968; Helling, 1971). Simazine exhibited low mobility in peat and peat moss (K_d more than 21) and a higher mobility in clay fractions (K_d values ranged from 0.0 for kaolinite to 12.2 for montmorillonite (Talbert and Fletchall, 1965). Freundlich K and n values were determined to be 7.25 and 0.88, respectively, for a silty clay loam soil.

- Simazine, as determined by soil TLC, is mobile to very mobile in sandy loam soil (R_f 0.80 to 0.96), and of low to intermediate mobility in loam and silty clay loam (R_f 0.45), sandy clay loam (R_f 0.51), silt loam (R_f 0.16 to 0.51), clay loam (R_f 0.32 to 0.45) and silty clay (R_f 0.36) soils. R_f values were positively correlated with soil organic matter and clay content (Helling and Turner, 1968; Helling, 1971).

- Based on results of soil column leaching studies, simazine phytotoxic residues were slightly mobile to mobile in soils ranging in texture from clay loam to sand (Harris, 1967; Ivey and Andrews, 1965; Rodgers, 1968). Upon application of 18 inches of water to 30-inch soil columns containing clay loam, loam, silt loam or fine sandy loam soils, simazine phytotoxic residues leached to depths of 4 to 6, 10 to 12, 22 to 24, and 26 to 28 inches, respectively (Ivey and Andrews, 1965).

- In field studies, simazine had a half-life of about 30 to 139 days in sandy loam and silt loam soils (Mattson et al., 1969; Martin et al., 1975; Walker, 1976). The degradate, 2-chloro-4-ethylamino-6-amino-s-triazine (G-28279) was detected at the 0- to 6-inch depth and at the 6- to 12-inch depth (Mattson et al., 1969; Martin et al., 1975).

- Simazine residues (uncharacterized) may persist up to 3 years in soil under aquatic field conditions. Dissipation of simazine in pond and lake water was variable, with half-lives ranging from 50 to 700 days. The degradation compound G-28279 was identified in lake water samples, but was no more persistent than the parent compound (Larsen et al., 1966; Flanagan et al., 1968; Kahrs, 1969; LeBaron, 1970; Smith et al., 1975; Kahrs, 1977).

- A recent review of simazine environmental fate is provided by Reinert and Rodgers (1987). This review may provide additional information to the data summarized in the above sections.

III. PHARMACOKINETICS

Absorption

- Orr and Simoneaux (1986) studied the metabolism of ^{14}C-simazine (uniformly labeled in the triazine ring) in groups of five male and five female Sprague-Dawley rats following oral administration in single doses at 0.5 or 200 mg/kg. At the low dose, 51 to 62% of the dose was eliminated as simazine equivalents in the urine and about 12% was found in the tissues, suggesting that about 63 to 74% (i.e., 0.315 to 0.37 mg/kg) of the dose was absorbed. At the high dose, only about 22% (i.e., 44 mg/kg) of the dose was found in urine and 2% (4 mg/kg) in the tissues of males or females. A third group of animals received daily single oral doses of unlabeled simazine at 0.5 mg/kg/day for 14 days followed by a single ^{14}C dose. Elimination of ^{14}C in urine ranged from 59 to 66% of the dose, and 8% was found in the tissues. Bakke and Robbins (1968) reported that, in goats and sheep, from 67 to 77% of a dose (the dose was not reported in this abstract) of ^{14}C-simazine (given orally in gelatin capsules) was excreted in urine. This suggests absorption was around 70%.

- Bakke and Robbins (1968) reported that in goats and sheep, from 67 to 77% of a dose of ^{14}C-simazine (given orally in gelatin capsules) was excreted in urine. This suggests that absorption was approximately 70%.

Distribution

- Orr and Simoneaux (1986) reported that 7 days following oral administration of ^{14}C-simazine to male and female Sprague-Dawley rats at 0.5 or 200 mg/kg, the highest ^{14}C residue levels, expressed as simazine equivalents found in the red blood cells, were 16.3 to 19.9 ppm at the high dose and 0.18 to 0.23 ppm at the low dose. Residue levels in red blood cells were slightly higher in males than in females. Lower concentrations were found in the other tissues ranging from 0.0 to 0.16 ppm at the low dose and from 0.78 to 5.2 ppm at the high dose. Relatively higher residues were found in the liver and kidney of rats receiving the low dose (0.1 to 0.16 ppm), with lower levels found in fat, plasma and bone (0.0 to 0.03 ppm). A similar pattern was observed in rats receiving the high dose, except that the spleen contained higher ^{14}C residues (4.1 to 5.2 ppm) than the liver and kidney (2.9 to 4.0 ppm). Residue levels in tissues of animals receiving the low ^{14}C dose following 14 days of repeated dosing were generally lower than those in rats receiving a single low dose, except in red blood cells. The authors suggested that repeated dosing with unlabeled simazine significantly reduced the number of available binding sites in all tissues, except the red blood cells.

- In rats receiving the high dose, ^{14}C residue levels, expressed as ppm, were 29-fold (kidney) to 516-fold (spleen) higher than those in animals receiving the low dose (Orr and Simoneaux, 1976).

Metabolism

- Simoneaux and Sy (1971) conducted a preliminary investigation on the metabolism of ^{14}C ring-labeled simazine found in the urine of female white rats. The rats were dosed once orally at 1.5 mg/kg, and the urine eliminated within 24 hours was collected and analyzed by thin-layer chromatography and thin-layer electrophoresis. The metabolites identified by comparison to authentic compounds were conjugated mercapturates of the following 3 metabolites: hydroxysimazine, 2-hydroxy-4-amino-6-ethylamino-s-triazine, and 2-hydroxy-4,6-diamino-s-triazine. These metabolites accounted for 6.8, 6.1 and 14% of the administered radioactivity, respectively. When the urine was hydrolized with performic acid (oxidizing agent) to cleave sulfur-carbon bonds of the conjugated mercapturates, prior to thin-layer chromatography, about 8.1, 7.7 and 31.3% of the radiolabel was detected as the three identified metabolites, respectively. Approximately half of the radioactivity in the urine was not identified.

° Bradway and Moseman (1982) administered simazine to male Charles River rats by gavage. Two doses of 0.017, 1.7, 17 or 167 mg/kg were given 24 hours apart. In 24-hour urine samples, the di-N-dealkylated metabolite (2-chloro-4,6-diamino-s-triazine) appeared to be the major product, ranging from 1.6% at the 1.7 mg/kg-dose to 18.2% at the 167-mg/kg dose, while the mono-N-dealkylated metabolite ranged from 0.35% at the 1.7-mg/kg dose to 2.8% at the 167-mg/kg dose.

° Guddewar and Dauterman (1979) purified glutathione S-transferase 61-fold from mouse liver. This enzyme conjugates chloro-s-triazine herbicides. A chloro group at the C2-position was found to be necessary for conjugation to occur. When this 2-chloro was replaced by a methylmercapto group, no conjugation occurred. The reaction rate decreased with triazine analogs lacking the alkyl side-chains. Atrazine was conjugated faster than either simazine or propazine.

° Similar results were obtained by Bohme and Bar (1967), who fed simazine (formulation and purity not stated) at levels of 200 or 800 mg/kg to albino rats and at 240 to 400 mg/kg to rabbits. Of the several metabolites identified, all retained the triazine ring intact. The principal species were the mono- and di-N-dealkylated metabolites.

° Bakke and Robbins (1968) administered ^{14}C-simazine orally by gelatin capsules to goats and sheep. The sheep were given simazine labeled on the triazine ring or on the ethylamino side-chain, while goats were given the ring-labeled compound only. Based on the metabolites identified in the urine of animals receiving the ring-labeled compound, there was no evidence to suggest that the triazine ring was metabolized. In sheep that received chain-labeled triazines, at least 40% of the ethylamino side-chains were removed. Using ion-exchange chromatography, 18 labeled metabolites were found in urine.

° Bohme and Bar (1967) and Larsen and Bakke (1975) observed that rat and rabbit urinary metabolites from the 2-chloro-s-triazines were all 2-chloro analogs of their respective parent molecules and none of the metabolites contained the 2-hydroxy moiety. Total N-dealkylation, partial N-dealkylation, and N-dealkylation with N-alkyl oxidation were suggested as the major routes of the metabolism of 2-chloro-s-triazines in rats and rabbits.

Excretion

- Orr and Simoneaux (1986) studied the metabolism of ^{14}C-simazine (uniformly labeled in the triazine ring) in Sprague-Dawley rats following oral administration in single doses. Males and females receiving 0.5 mg/kg eliminated 50.5 and 62.1% of the dose, respectively, in the urine, and 19.1 and 13.3% of the dose in the feces, 7 days after dosing. In animals receiving a single dose of ^{14}C-simazine following repeated dosing at 0.5 mg/kg/day for 14 days with unlabeled simazine, males eliminated 58.5 and 24.5% of the dose in the urine and feces, respectively, whereas females eliminated 66.0 and 17.8% of the dose. A third group of males and females receiving a single dose of 200 mg/kg eliminated about 21% of the dose in the urine and about 2.0% in the feces. The elimination pattern with time after dosing was biphasic with rates being faster in females than males. Most of the radioactivity was eliminated in 72 hours with a half-life of 9 to 15 hours. Elimination of the remaining radioactivity occurred at a slower rate with half-life values ranging from 21 to 32 hours.

- In a preliminary study with two female white rats dosed orally at 1.5 mg/kg ring-labeled ^{14}C-simazine, Simoneaux and Sy (1971) found less than 0.05% of the dose being eliminated as ^{14}C-carbon dioxide 96 hours after dosing. Approximately 49.3% of the dose was eliminated in the urine and 40.8% in the feces.

- Bakke and Robbins (1968) studied the excretion of simazine in goats and sheep using triazines labeled with ^{14}C on the ring or on the ethylamino sidechains. No $^{14}CO_2$ was detected from animals that received the ring-labeled compounds, which suggested that the triazine ring was not metabolized. Approximately 67 to 77% of the administered ring-labeled activity was found in the urine, and 13 to 25% was found in the feces. About 0.16 ppm of ^{14}C residues were present in the milk immediately after dosing, but the level decreased to 0.04 ppm within 48 hours.

- St. John et al. (1965) fed unlabeled simazine (5 ppm) to a lactating cow for 3 days. Urine and milk were collected and analyzed during the feeding period and for 3 days thereafter. No simazine was detected in the milk (sensitivity of method approximately 0.1 ppm), and only about 1% of the administered simazine was excreted in the urine as the parent compound. Milk, excreta and body tissues were not analyzed for simazine metabolites.

- Hapke (1968) reported that simazine residues were present in the urine of sheep for up to 12 days after administration of a single oral dose. The maximum concentration in the urine occurred from 2 to 6 days after administration.

IV. HEALTH EFFECTS

Humans

- There were 124 cases of contact dermatitis noted by Yelizarov (1977) in the Soviet Union among workers manufacturing simazine and propazine. Mild cases lasting 3 or 4 days involved pale pink erythema and slight edema. Serious cases lasting 7 to 10 days involved greater erythema and edema and a vesiculopapular reaction that sometimes progressed to the formation of bullae.

Animals

Short-term Exposure

- Oral LD_{50} values for simazine have been reported to be greater than 5,000 mg/kg in the rat (Martin and Worthing, 1977), the mouse and the rabbit (USDA, 1984).

- Mazaev (1964) administered a single oral dose of simazine (formulation and purity not stated) to rats at 4,200 mg/kg. Anorexia and weight loss were observed, with some of the animals dying in 4 to 10 days. When 500 mg/kg was administered daily, all the animals died in 11 to 20 days, with the time of death correlating with the loss of weight.

- Sheep and cattle seem to be much more susceptible than laboratory animals to simazine toxicity. Hapke (1968) reported that a single oral dose of simazine, 50% active ingredient (a.i.), as low as 500 mg/kg was fatal to sheep within 6 to 25 days after administration. The animals that survived the exposure were sick for 2 to 4 weeks after treatment and showed loss of appetite, increased intake of water, incoordination, tremor and weakness. Some of the animals exhibited cyanosis and clonic convulsions.

- Palmer and Radeleff (1969) orally exposed cattle by drench to 10 doses of simazine 80W (purity not stated) at 10, 25 or 50 mg/kg/day and sheep by drench or capsule to 10 doses at 25, 50, 100 or 250 mg/kg. The number of test animals in each group was not stated, and the use of controls was not indicated. Anorexia, signs of depression, muscle spasms, dyspnea, weakness and uncoordinated gait were commonly observed in treated animals. Necropsy showed congestion of lungs and kidneys, swollen, friable livers, and small, hemorrhagic spots on the surface of the lining of the heart.

- Palmer and Radeleff (1964) found that repeated oral administration of simazine 80W (purity not stated) at either 31 daily doses of 50 mg/kg or 14 daily doses of 100 mg/kg was fatal to sheep. Simazine was also lethal when administered at 100 mg/day for 14 days by drench (Palmer and Radeleff, 1969).

- The acute inhalation LC_{50} value of simazine is reported to be more than 2.0 mg/L of air (4-hour exposure) (Weed Science Society of America, 1983).

Dermal/Ocular Effects

- The acute dermal toxicity in rabbits is greater than 8,000 mg/kg (NAS, 1977).

- In a 21-day subacute dermal toxicity study in rabbits, Ciba-Geigy (1980) reported that 15 dermal applications of technical simazine at doses up to 1 g/kg produced no systemic toxicity or any dose-related alterations of the skin.

- In primary eye irritation studies in rabbits, simazine caused transient inflammation of conjunctivae, but was not irritating to the iris or cornea (USDA, 1984).

Long-term Exposure

- Tai et al. (1985a) conducted a 13-week subacute oral toxicity study in Sprague-Dawley rats fed technical simazine at 0, 200, 2,000 or 4,000 ppm in their diets. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0, 10, 100 or 200 mg/kg/day. Significant dose-related reductions in food intake, mean body weight and weight gain occurred in all treated groups. Significant weight loss occurred in mid- and high-dose animals during the first week of dosing. At 13 weeks, various dose-related effects were noted in hematological parameters (decreased mean erythrocyte and leukocyte counts and increased neutrophil and platelet counts), clinical chemistry (lowered mean blood glucose, sodium, calcium, blood urea nitrogen (BUN), lactic dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (SGOT) and creatinine and increased cholesterol and inorganic phosphate levels), and urinalysis determinations (elevated ketone levels and decreased protein levels). Relative and absolute adrenal, brain, heart, kidney, liver, testes and spleen weights increased, and overy and heart weights decreased. Necropsies revealed no gross lesions attributable to simazine. A dose-related incidence of renal calculi and renal epithelial hyperplasia were detected microscopically in treated rats, primarily in the renal pelvic lumen and rarely in the renal tubules. Microscopic examinations revealed no other lesions that could be attributed to simazine. It appeared to the authors that reduced mean food intake in treated rats was most likely due to the unpalatability of simazine. Lower individual body weights and reduced body weight gains paralleled mean food intake in treated rats. The majority of the alterations in clinical chemistry values may have been related to reduced food consumption. Since these dietary levels of simazine seriously affected the nutritional status of treated rats, the results of this study are of limited value.

- Tai et al. (1985b) also conducted a 13-week dietary study with beagle dogs fed technical simazine at 0, 200, 2,000 or 4,000 ppm. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day, Lehman (1959), these levels correspond to doses of about 0, 5, 50 or 100 mg/kg/day. As in the previously described study in rats, reduced daily food consumption was attributed to the palatability of simazine in the diet and corresponded with weight loss, decreased weight gain and various effects on hematology, clinical chemistry, and urinalysis determinations. Changes in these parameters were generally similar to those noted in the rat study (Tai et al., 1985a). Due to the seriously affected nutritional status of the test animals, the results of this study are of limited value.

- Dshurov (1979) studied the histological changes in the organs of 21 sheep following exposures to simazine (50% a.i.) by gavage at 0, 1.4, 3.0, 6.0, 25, 50, 100 or 250 mg/kg/day for various time durations up to about 22 weeks. Fatty and granular liver degeneration, diffuse granular kidney degeneration, neuronophagia, diffuse glial proliferation and degeneration of ganglion cells in the cerebrum and medulla were found. In sheep that died, spongy degeneration, hyperemia and edema were observed in the cerebrum; the degree of severity was related to the dose of simazine and the duration of exposure. The thyroid showed hypofunction after daily doses of 1.4 to 6.0 mg/kg was administered for periods of 63 to 142 days. The most severe antithyroid effect followed one or two doses of 250 mg/kg, which in one sheep produced parenchymatous goiter and a papillary adenoma. This type of goiter was also seen in sheep administered simazine at 50 or 100 mg/kg once per week for approximately 22 weeks. Based on these data, a Lowest-Observed-Adverse-Effect Level (LOAEL) of 1.4 mg/kg can be identified; however, it is not clear from the study whether the authors considered the 50% formulation when providing the dosage levels.

Reproductive Effects

- Woodard Research Corporation (1965) reported that no adverse effects on reproductive capacity were observed in a three-generation study in rats. In this study, two groups of 40 weanling rats (20/sex) were used; one served as the control and the other was fed simazine 80W at 100 ppm. This corresponds to a dose of about 5 mg/kg/day, based on the assumptions that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959). After 74 days of dosing, animals were paired and mated for 10 days, resulting in F_{1a} litters. After weaning first litters, parents were remated to produce F_{1b} litters. Weanlings of parents in the 100 ppm group were divided into two groups and fed simazine at 50 ppm (approximately 2.5 mg/kg/day) or at 100 ppm. After 81 days they were mated to produce the F_{2a} and F_{2b} litters. F_{2b} weanlings were fed the same dietary levels of simazine (0, 50 or 100 pp[illegible] $_{2b}$ rats were mated to produce F_{3a} and F_{3b} litters. Reproductive performance of rats fed simazine was basically similar to that of controls, and no developmental changes were detected. The No-Observed-Adverse-Effect Level (NOAEL) for this study is approximately 5 mg/kg/day.

- Dshurov (1979) reported that repeated administration of simazine (50% a.i.) to sheep (6.0 mg/kg for 142 days or 25 mg/kg for 37 to 111 days) caused changes in the germinal epithelium of the testes and disturbances of spermatogenesis.

Developmental Effects

- Simazine (97% a.i.) was administered by gavage to a group of 19 New Zealand White rabbits (2.5 to 4.5 kg) at daily doses of 5, 75 or 200 mg/kg for days 7 through 19 of presumed gestation (Ciba-Geigy, 1984). The herbicide was delivered as a suspension in 3% cornstarch containing 0.5 percent Tween 80. A control group was given the vehicle only. One death was observed in each group; however, death of the low-dosed dam was assumed to be due to a dosing accident and not compound-related. Maternal toxicity at 75 and 200 mg/kg was indicated by abortions, tremors, decreased motor control and activity, ataxia (in one high-dosed animal), few or no stools, anorexia, weight loss, and decreased body weight gain. Embryotoxicity was not oberved, but fetal toxicity, which was believed to be the consequence of maternal toxicity, was evident in the intermediate- and high-dose groups as indicated by decreased numbers of viable fetuses. Fetal toxicity at 200 mg/kg was also reflected by reduced fetal body weights, increased occurrence of floating and fully formed ribs, and decreased ossification of the patellae. No malformations were associated with any dose level of simazine, and at 5 mg/kg the herbicide exerted neither toxic nor teratogenic effects. The authors concluded that at doses of 75 mg/kg/day and higher, simazine was very toxic to fetuses and dams but was neither embryotoxic nor teratogenic.

- Chen (1981) studied the teratogenic effects of simazine in rats. The herbicide was administered by gastric intubation to pregnant rats from the 6th to 15th day of gestation at dose levels of 78, 312, 1,250 and 2,500 mg/kg bw/day. Ossification of the sternum and cranium was delayed at all four dose levels. At doses of 312 mg/kg and above, body weight gain was inhibited in the dams, the number of live fetuses was reduced, and the rate of fetal resorption increased. At the higher dose level (2,500 mg/kg), simazine caused delayed fetal development. The author concluded that simazine was toxic to rat embryos but was not teratogenic.

- No treatment-related developmental effects were observed by Newell and Dilley (1978) in the offspring of rats exposed to simazine at 0, 17, 77 and 317 mg/m^3 via inhalation for 1 to 3 hours/day on days 7 through 14 of gestation.

Mutagenicity

- Simazine has shown negative results in a variety of microbial mutagenicity assay systems including tests with the following organisms: *Salmonella typhimurium* (Simmons et al., 1979; Eisenbeis et al., 1981; Anderson et al., 1972); *Escherichia* *coli* (Simmons et al., 1979; Fahrig, 1974); *Bacillus subtilis* (Simmons et al., 1979); *Serratia marcescens* (Fahrig, 1974); and *Saccharomyces cerevisiae* (Simmons et al., 1979).

- Simazine induced lethal mutations in the sex-linked recessive lethal test using the fruitfly *Drosophila melanogaster* (Valencia, 1981). In a study reported by Murnik and Nash (1977), simazine increased X-linked lethals when injected into male *D. melanogaster*, but failed to do so when fed to larvae.

- There are contradictory data concerning the ability of simazine to cause DNA damage. According to Simmons et al. (1979), simazine induced unscheduled DNA synthesis in a human lung fibroblast assay. However, in the same test conducted by Waters et al. (1982), simazine showed a negative response.

- Simazine does not produce chromosomal effects as indicated by the sister-chromatid exchange test and mouse micronucleus assay (Waters et al., 1982).

Carcinogenicity

- Simazine was not tumorigenic in an 18-month feeding study in mice at the highest tolerated dose of 215 mg/kg/day (Innes et al., 1969). In this bioassay of 120 compounds, male and female mice of two hybrid strains (C57BL/6 x C3H/Anf)F_1 and (C57BL/6 x AKR)F_1 were exposed to simazine (purity not stated) at the maximum tolerated dose of 215 mg/kg by gavage from ages 7 to 28 days. For the remainder of the study, the animals were maintained on a diet with simazine at 215 mg/kg/day. Based on information presented only in tabular form, gross necropsy and histological examination revealed no significant increase in tumors related to treatment with simazine. Other toxicological data were not provided. This study is not considered to provide adequate data to fully assess the carcinogenic potential of simazine.

- Hazelton Laboratories (1960) conducted a 2-year dietary study in Charles River rats administered simazine 50W (49.9% a.i.) in the feed at 0, 1, 10 and 100 ppm (expressed on the basis of 100% a.i.). Based on the dietary assumptions of Lehman (1959), these levels are equivalent to approximately 0, 0.05, 0.5 and 5 mg/kg/day. These authors reported an excess of thyroid and mammary tumors in high-dose females. However, complete histopathological details were not provided and statistical significance was not evaluated. Furthermore, the high incidence of respiratory and ear infections in all groups renders this study unsuitable for evaluating the carcinogenic potential of simazine.

- Simazine was found to produce sarcomas at the site of subcutaneous injection in both rats and mice (Pliss and Zabezhinsky, 1977; abstract only).

- An interim report by Ciba-Geigy Corporation (1987) on a new chronic feeding/oncogenicity study in Sprague-Dawley rats indicates that simazine may cause mammary gland tumors. However, when this study is complete, an evaluation of these data will be performed.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA and NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable studies were found in the available literature for the determination of the One-day HA value for simazine. It is therefore recommended that the Ten-day HA of 0.5 mg/L (500 ug/L) calculated below be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

No suitable studies were found in the available literature for the determination of the Ten-day HA value for simazine, with the exception of a rabbit teratology study by Ciba-Geigy (1984. In this study, simazine was administered by gavage to female rabbits during gestation days 7 to 19 (13 days). A NOAEL of 5 mg/kg/day for maternal toxicity was established and a LOAEL of 75 mg/kg/day was noted based on abortions and tremors, decreased motor control and activity, anorexia and weight loss. The NOAEL of 5 mg/kg/day in the rabbit is selected for use as the basis for calculation of the Ten-day HA.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(5.0\ \text{mg/kg/day})\ (10\ \text{kg})}{(1\ \text{L/day})\ (100)} = 0.5\ \text{mg/L}\ (500\ \text{ug/L})$$

where:

5.0 mg/kg/day = NOAEL, based on the absence of adverse effects in female rabbits given simazine by gavage during days 7 to 19 of gestation.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

10 kg = assumed body weight of a child.

1 L/day = assumed water consumption of a 10-kg child.

Longer-term Health Advisory

No suitable studies were found in the available literature for the determination of the Longer-term HA values for simazine. It is therefore recommended that the adjusted DWEL of 0.05 mg/L (50 ug/L) be used at this time as a conservative estimate of the Longer-term HA value for a 10-kg child and that the DWEL of 0.2 mg/L (200 ug/L) be used for a 70-kg adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The three-generation reproduction study in rats by Woodard Research Corporation (1965) has been selected to serve as the basis for calculation of the DWEL and Lifetime HA for simazine. In this study, two groups of 40 weanling rats (20/sex) were used; one served as the control, and the other was fed simazine 80W at 100 ppm (approximately 5 mg/kg/day). After 74 days of dosing, animals were paired and mated for 10 days, resulting in F_{1a} litters. After weaning first litters, parents were remated to produce F_{1b} litters. Weanlings of parents in the 100 ppm group were divided into two test groups: one group was fed simazine at 50 ppm (about 2.5 mg/kg/day) and the other at 100 ppm. After 81 days of dosing, animals were mated to produce the F_{2a} and F_{2b} litters. The F_{2b} weanlings were then divided into 50- and 100-ppm dosage groups. F_{2b} rats were mated to produce F_{3a} and F_{3b} litters. Reproductive performance of rats fed simazine was the same as that of controls, and no teratological changes were detected. The NOAEL for this study is 5 mg/kg/day.

It is important to note that, in this study, rats in the F_0 generation were exposed to simazine at the high dose (100 ppm) only. However, considering that the F_1 and F_2 generations treated with 100 ppm did not reflect any adverse reproductive effects, this feature of the study design did not seem to affect the results. Therefore, the NOAEL of 5 mg/kg/day is used for calculation of the RfD.

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{5\ \text{mg/kg/day}}{(1{,}000)} = 0.005\ \text{mg/kg/day}$$

where:

5 mg/kg/day = NOAEL for reproductive and developmental effects in a three-generation rat study.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.005\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.175\ \text{mg/L}\ (200\ \text{ug/L})$$

where:

0.005 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(0.175\ \text{mg/L})\ (20\%)}{10} = 0.0035\ \text{mg/L}\ (4\ \text{ug/L})$$

where:

0.175 mg/L = DWEL

20% = Assumed relative source contribution from water.

10 = additional uncertainty factor, according to ODW policy, to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- An interim report by Ciba-Geigy Corporation (1987) on a new chronic feeding/oncogenicity study in Sprague-Dawley rats indicates that simazine reflects some oncogenic activity in the mammary glands as previously noted with atrazine and propazine. Apparently this positive study has been completed recently and submitted to the Office of Pesticide Programs. An evaluation of this study will be performed in the near future. Neither the study in mice by Innes et al. (1969) nor the study in rats by Hazelton Laboratories (1960) is considered adequate for assessment of the carcinogenicity of this substance. However, the Hazelton rat study (1960) still reflected a potential positive oncogenic effect in the same target organ, the mammary glands.

- Simazine is a chloro-s-triazine derivative, with a chemical structure analogous to atrazine and propazine. Both of these structurally-related compounds were found to significantly ($p > 0.05$) increase the incidence of mammary tumors in rats. The structure-activity relationship of this group of chemicals indicates that simazine is likely to reflect a similar pattern of oncogenic response in rats as atrazine and propazine.

- Applying the criteria described in EPA's guidelines for the assessment of carcinogenic risk (U.S. EPA, 1986a), simazine may be preliminarily classified in Group C: possible human carcinogen. This category is used for substances with limited evidence of carcinogenicity in animals in the absence of human data. This classification is considered preliminary until the Office of Pesticide Programs completes a peer review of the weight of the evidence for simazine and its analogs.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- A tolerance level of 10 ug/L has been established for simazine and its metabolites in potable water when present as a result of application to growing aquatic weeds (U.S. FDA, 1979).

- Residue tolerances have been established for simazine alone and the combined residues of simazine and its metabolites in or on various raw agricultural commodities (U.S. EPA, 1986b). These tolerances range from 0.02 ppm (negligible) in animal products to 15 ppm in various animal fodders.

VII. ANALYTICAL METHODS

- Analysis of simazine is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, Method #507, approximately 1 L of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen-phosphorus detector. The method detection limit has not been determined for the analytes in this method, including simazine. The estimated detection limit is 0.075 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove simazine from water include activated carbon adsorption; ion exchange; and chlorine, chlorine dioxide, ozone, hydrogen peroxide and potassium permanganate oxidation. Conventional treatment processes were relatively ineffective in removing simazine (Miltner and Fronk, 1985a). Limited data suggest that aeration would not be effective in simazine removal (ESE, 1984; Miltner and Fronk, 1985a).

- Baker (1983) reported that a 16.5-inch GAC filter cap using F-300, which was placed upon the rapid sand filters at the Fremont, Ohio water treatment plant and had been in service for 30 months, reduced the simazine levels by 35 to 89% in the water from the Sandusky River. Miltner and Fronk (1985a) developed adsorption capacity data using spiked, distilled water treated with Filtrasorb 400. The following Freundlich isotherm values were reported for simazine: K = 490 mg/g; 1/n = 0.56.

- At the Bowling Green, Ohio water treatment plant, PAC in conjunction with conventional treatment achieved an average reduction of 47% of the simazine levels in the water from the Maumee River (Baker, 1983). Miltner and Fronk (1985b) monitored simazine levels at water treatment plants, which utilized PAC, in Bowling Green and Tiffin, Ohio. Applied at dosages ranging from 3.6 to 33 mg/L, the PAC achieved 43 to 100% removal of simazine with higher percent removals reflecting higher PAC dosages. Andersen (1968) reported that activated charcoal (wood charcoal, 300-mesh A.C. from Harrison Clark, Ltd.) was effective in "inactivating" simazine when mixed into simazine-treated soils, although no quantitative data on simazine concentrations were reported.

- Rees and Au (1979) reported that an adsorption column containing XAD-2 resin removed 81 to 95% of the simazine in spiked tap water.

- Turner and Adams (1968) reported that, in a study on the adsorption of simazine by ion exchange resins (Sheets, 1959), duolite C-3 cation exchange resin removed from solution up to 2,000 ug of simazine per gram of resin. Little adsorption was observed with Duolite A-2 anion exchange resin.

- Miltner and Fronk (1985b) reported the bench scale testing results of the addition of various oxidants to spiked, distilled water. Chlorine oxidation achieved 62 to 74 percent removal of simazine. However, when spiked Ohio River water was treated with smaller chlorine dosages during shorter time intervals, less than 17% removal was achieved. Chlorine dioxide oxidation of spiked, distilled water achieved only a 22% removal and achieved 8 to 27% removal of simazine in spiked Ohio River water when applied at a smaller dosage over a shorter time interval. Ozonation of spiked, distilled water resulted in a 92% removal of simazine. Oxidation of spiked, distilled water with hydrogen peroxide obtained a 19 to 42% removal of simazine, and in spiked Ohio River water, a smaller dosage over a shorter time interval obtained a simazine removal of 1 to 25%. Potassium permanganate oxidized up to 26% of the simazine present in spiked distilled water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

2,4,5-TRICHLOROPHENOXYACETIC ACID

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

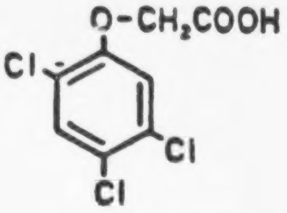
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 93-76-5

Structural Formula



2,4,5-trichlorophenoxyacetic acid

Synonyms

- 2,4,5-T; Dacamine; Ded-Weed; Fencerider; Forron; Inverton 245; Linerider; T-Nox; U-46 (Meister, 1988).

Uses

- The use of 2,4,5-T in the United States has been cancelled since 1985. Some or all applications may be classified by the U.S. EPA as Restricted Use Pesticides (Meister, 1988).

Properties (BCPC, 1983; Meister, 1983; Windholz et al., 1983; Khan, 1985; CHEMLAB, 1985)

Chemical Formula	$C_8H_5O_3Cl_3$
Molecular Weight	255.49
Physical State (25°C)	Crystals
Boiling Point	--
Melting Point	153°C
Density	--
Vapor Pressure (25°C)	6.46×10^{-6} mm Hg
Specific Gravity	--
Water Solubility (25°C)	Solubility of acid is 150 g/L; amine salts are soluble at 189 g/L (20°C); esters are insoluble
Log Octanol/Water Partition Coefficient	3.00 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- 2,4,5-T has been found in 4,021 of 21,616 surface water samples analyzed and in 99 of 2,905 ground water samples (STORET, 1988). Samples were collected at 3,838 surface water locations and 1,853 ground water locations, and 2,4,5-T was found in 44 states. The 85th percentile of all nonzero samples was 0.1 ug/L in surface water and 1 ug/L in ground water sources. The maximum concentration found was 370 ug/L in surface water and 38 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Salts dissociate in aqueous media, and esters are rapidly hydrolized to acids by enzymatic action in animals, plants, and soil (Loos, 1975).

- The phenoxy ether link is stable in plants and animals, but is cleaved by bacterial action in soil and in the rumen of cattle and sheep (Leng, 1977). The rate of cleavage is inhibited by substitution of a third chlorine at the meta position on the ring and is sterically hindered by the angular methyl group in the 2-propionic acid side-chain.

- The first step in degradation of chlorophenoxy acids and chlorophenols occurs by hydroxylation at the 4-position with shift of the 4-chloro group to the 3- or 5-position (NIH shift). This reaction also is inhibited by the presence of a m-chloro substituent; thus, residues of 2,4,5-trichlorophenol appeared in the milk of cows and in the liver and kidney of cattle maintained on feed containing 100 or 300 ppm 2,4,5-T, respectively (Leng, 1977).

- The rate of microbial degradation of chlorophenoxyalkanoic acids in the environment depends on a number of factors, including sunlight, temperature, moisture and organic matter in soil, and whether the organisms were adapted by repeated treatment (Loos, 1975; NRCC, 1978; Bovey and Young, 1980). Under field conditions favorable for degradation, 2,4-D disappears within about 2 to 3 weeks, whereas other phenoxy herbicides disappear more slowly (Loos, 1975). The average half-lives in a laboratory study were 4, 10, 17 and 20 days for 2,4-D, dichloroprop, fenoprop, and 2,4,5-T, respectively, when added as dimethylamine salts at about 5 ppm in three soils containing partially decomposed litter obtained from two forest sites and one grassland site in Oklahoma (Altom and Stritzke, 1973).

- Photodegradation is rapid when phenoxy herbicides are exposed to sunlight in water containing dissolved organic matter, and the resultant chlorophenols are photolyzed even more rapidly than the parent acids (NRCC, 1978; Bovey and Young, 1980). The dioxin impurity TCDD is also degraded rapidly by sunlight, particularly in the presence of its herbicide carrier on the surface of leaves or in the presence of other hydrogen donors dissolved in water (NRCC, 1978).

- Plants treated with phenoxy herbicides rapidly hydrolyze esters and salts to the parent acids, which form ether-soluble conjugates with amino acids or water-soluble conjugates with sugars, depending on the relative susceptibility or resistance of the plants to the herbicides (Loos, 1975).

III. PHARMACOKINETICS

Absorption

- In a study by Gehring et al. (1973), single oral doses of 5 mg/kg 2,4,5-T were ingested by five male volunteers. Essentially all the 2,4,5-T was excreted unchanged via the urine, indicating that gastrointestinal absorption was nearly complete.

- Fang et al. (1973) administered single doses of ^{14}C-labeled 2,4,5-T in corn oil by gavage to pregnant and nonpregnant female Wistar rats at dose levels of 0.17, 4.3 or 41 mg/kg. Expired air, urine, feces, internal organs and tissues were analyzed for radioactivity. During the first 24 hours, an average of 75 ±7% of the radioactivity was excreted in the urine, indicating that at least 75% of the dose had been absorbed.

- Piper et al. (1973) administered single oral doses of ^{14}C-labeled 2,4,5-T in corn oil-acetone (9:1) to adult female Sprague-Dawley rats at dose levels of 5, 50, 100 or 20 mg/kg, and to adult female beagle dogs at 5 mg/kg. Fecal excretion was 3% at the lowest dose (5 mg/kg) and increased to 14% at the highest dose (200 mg/kg) in rats. In dogs given the 5 mg/kg dose, fecal excretion was 20%. These data indicated that absorption was somewhat dose dependent, but was 80% or higher at all doses.

Distribution

- Gehring et al. (1973) administered single oral doses of 5 mg/kg of 2,4,5-T to five male volunteers. Essentially all the 2,4,5-T was absorbed; 65% of the absorbed dose remained in the plasma where 98.7% was bound reversibly to protein. The volume of distribution was 0.097 L/kg. Utilizing the kinetic constants from the single-dose experiment, the expected concentrations of 2,4,5-T in the plasma of individuals receiving repeated doses of 2,4,5-T were calculated. From these calculations, it was determined that the plasma concentrations would essentially reach a plateau value after 3 days. If the daily dose ingested in mg/kg is A_0, the concentrations in the plasma after attaining plateau would range from 12.7 A_0 to 22.5 A_0 ug/mL (Gehring et al., 1973).

- Fang et al. (1973) administered single oral doses of ^{14}C-labeled 2,4,5-T to pregnant and nonpregnant female Wistar rats and internal organs and tissues were analyzed for radioactivity. Radioactivity was detected in all tissues, with the highest concentration found in the kidney. The maximum concentration in all tissues was generally reached between 6 and 12 hours after administration of the dose

(0.17, 4.3 or 41 mg/kg) by gavage, and then declined rapidly. Radioactivity also was detected in the fetuses and in the milk of the pregnant rats. The average biological half-life of 2,4,5-T in the organs was 3.4 hours for the adult rats and 97 hours for the newborn.

° Piper et al. (1973) administered single oral doses of 5, 50, 100 or 200 mg/kg 2,4,5-T to Sprague-Dawley rats, and found that the apparent volume of distribution increased with dose, indicating that distribution of 2,4,5-T in the body was dose-dependent.

Metabolism

° Gehring et al. (1973) administered single oral doses of 5 mg/kg 2,4,5-T to human volunteers. Essentially all the chemical was excreted in the urine as parent compound, indicating that there is little metabolism of 2,4,5-T in humans.

° Grunow et al. (1971) investigated the metabolism of 2,4,5-T in male Wistar (AF/Han) rats which received single oral doses of 50 mg/kg. The 2,4,5-T was dissolved in peanut oil and administered by gavage. Urine was collected for 7 days after dosing and examined by gas chromatography for 2,4,5-T and its conjugates and metabolites. From 45 to 70% of the administered dose was recovered in urine. In general, about 10 to 30% of this was as acid-hydrolyzable conjugates, and the remainder was unchanged 2,4,5-T. Three animals were given doses of 75 mg/kg, and their urine pooled. A metabolite isolated from this pooled urine was identified as N-(2,4,5-trichlorophenoxy-acetyl)glycine.

° Piper et al. (1973) administered single oral doses of 2,4,5-T to female Sprague-Dawley rats at dose levels of 5, 50, 100 or 200 mg/kg. A small amount of an unidentified metabolite was detected in urine at the high doses, but not at the lower doses. In adult beagle dogs given oral doses of 5 mg/kg, three unidentified metabolites were detected in urine, suggesting a difference in metabolism between rats and dogs.

° In a study by Fang et al. (1973) in female Wistar rats, urinalysis revealed that 90 to 95% of the radioactivity was unchanged 2,4,5-T. The authors also found three unidentified minor metabolites, two of which were nonpolar, in the urine.

Excretion

° In a study by Gehring et al. (1973), single doses of 5 mg/kg 2,4,5-T were ingested by five male volunteers. The concentrations of 2,4,5-T in plasma and its excretion were measured at intervals after ingestion. The clearances from the plasma, as well as the body, occurred via apparent first-order rate processes with half-lives of 23.1 and 29.7 hours, respectively. Essentially all the 2,4,5-T was excreted unchanged via the urine.

° In a study by Fang et al. (1973), 2,4,5-T labeled with ^{14}C was orally administered to pregnant and nonpregnant female Wistar rats at various dosages, and expired air, urine and feces were analyzed for radioactivity. During the first 24 hours, 75 ± 7% of the radioactivity was excreted in the urine and 8.2% was excreted in the feces. No ^{14}C was found in the expired air. There was no significant difference in the rate of elimination between the pregnant and nonpregnant rats, or among the dosages used (0.17, 4.3 and 41 mg/kg). The average biological half-life of 2,4,5-T in the organs was 3.4 hours for the adult rats and 97 hours for the newborn.

- Grunow et al. (1971) investigated the excretion of 2,4,5-T in male Wistar (AF/Han) rats after single oral doses of 50 mg/kg. The 2,4,5-T was dissolved in peanut oil and administered by gavage. From 45 to 70% of the administered dose was recovered in urine within 7 days.

- Clearance of ^{14}C activity from the plasma and its elimination from the body of rats and dogs were determined after single oral doses of labeled 2,4,5-T (Piper et al., 1973). The half-life values for clearance from the plasma of Sprague-Dawley (Spartan strain) rats given doses of 5, 50, 100 or 200 mg/kg were 4.7, 4.2, 19.4 and 25.2 hours, respectively; half lives for elimination from the body were 13.6, 13.1, 19.3 and 28.9 hours, respectively. Urinary excretion of unchanged 2,4,5-T accounted for 68 to 93% of the radioactivity eliminated from the body of the rats. Fecal excretion was 3% at 5 mg/kg, and increased to 14% at 200 mg/kg. These results indicate that the excretion of 2,4,5-T is altered when large doses are administered. In adult beagle dogs given doses of 5 mg/kg, the half-life values for clearance from plasma and elimination from the body were 77.0 and 86.6 hours, respectively. By 9 days post-treatment, 11% of the dose had been recovered in urine and 20% had been recovered in feces.

IV. HEALTH EFFECTS

- Technical 2,4,5-T contains traces of the highly toxic compound 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as an impurity (NAS, 1977). Preparations of 2,4,5-T formerly contained TCDD at levels of 1 to 80 ppm, a concentration sufficiently high to cause toxic effects that are characteristic of TCDD. It has not been feasible to completely eliminate TCDD from technical 2,4,5-T, but NAS (1977) reported it to be present in commercial 2,4,5-T at less than 0.1 ppm. In the following sections, the purity of 2,4,5-T or the level of TCDD impurity is given when known. When the generic term "dioxin" is used, no further information was provided, and the 2,4,5-T is presumed to contain a variety of dioxin species as well as other phenoxy compounds and assorted intermediates and breakdown products.

Humans

Short-term Exposure

- No clinical effects were observed in five volunteers who ingested single oral doses of 5 mg/kg of 2,4,5-T (Gehring et al., 1973).

- After an explosion in a chemical plant producing 2,4,5-T in 1949, symptoms in exposed workers included chloracne, nausea, headache, fatigue, and muscular aches and pains (Zack and Suskind, 1980).

Long-term Exposure

- The mortality experience in a cohort of 1,926 men who had sprayed 2,4,5-T acid during 1955 to 1971 was followed prospectively from 1972 to 1980. Exposure was generally rather low because the duration of work had mostly been less than 2 months. In the period 1972 to 1976, mortality from all natural causes in this group was only 54% of the expected value (based on age-specific rates for the general population), and in the next 4-year period, 81% of the expected value. In the assessment of cancer, mortality allowance was made for 10- and 15-year periods of latency between the first exposure and the start of the recording of vital status during the followup. No increase in cancer mortality was detected, and the distribution of cancer types was unremarkable. No cases of death from lymphomas or soft tissue sarcomas were found. It was noted, however, that the study results should be interpreted with caution due to the small size of the cohort, the low past exposure, and the brief followup period (Riihimaki et al., 1982).

- An investigation of the rate of birth malformations in the Northland region of New Zealand was analyzed with reference to the exposure in the area to 2,4,5-T, which was applied as frequently as once a month from 1960 to 1977. The chosen area was divided into sectors rated as high, intermediate or low, based on the frequency of aerial spraying. During this period, there were 37,751 babies born in the hospitals in these sectors. It was estimated that well over 99% of all births occur in hospitals in this Northland area. The epidemiological analysis of the birth data gave no evidence that any malformation of the central nervous system, including spina bifida, was associated with the spraying of 2,4,5-T. Heart malformations, hypospadias, and epispadias increased with spraying density, but the increases were not statistically significant ($p > 0.05$). The only anomaly that increased in a statistically significant ($p < 0.05$) manner with respect to the spraying was talipes (club foot) (Hanify et al., 1981).

- The relationship between the use of 2,4,5-T in Arkansas and the concurrent incidence of facial clefts in children was studied retrospectively. The estimated levels of exposure were determined by categorizing the 75 counties into high, medium and low exposure groups on the basis of their rice acreage during 6- to 7-year intervals beginning in 1943. A total of 1,201 cases of cleft lip and/or cleft palate for the 32 years (until 1974) was detected by screening birth certificates and hospital records. Facial cleft rates, presented by sex, race, time period and exposure group, generally rose over time. No significant differences were found for any race or sex combination. The investigators concluded that the general increase seen in facial cleft incidence in the high- and low-exposure groups was attributable to better case finding rather than maternal exposure to 2,4,5-T (Nelson et al., 1979).

- Ott et al. (1980) reported no effects in a survey of 204 workers engaged in 2,4,5-T production at estimated airborne levels of 0.2 to 0.8 mg/m^3 for 1 month to 10 years.

- Numerous epidemiological studies on the relationship between exposure to chlorophenoxyacetic acids and cancer induction are reviewed in U.S. EPA (1985). The conclusion in this review is that there is "limited" evidence for the carcinogenicity of chlorinated phenoxyacetic herbicides and/or chlorophenols with chlorinated dibenzodioxin impurities, primarily based on Swedish case-control studies that associated induction of soft-tissue sarcomas with exposure to these agents.

Animals

Short-term Exposure

- The acute oral toxicity of 2,4,5-T was determined in mice, rats and guinea pigs by Rowe and Hymas (1954) over a 2-week period. The LD_{50} values were 500 mg/kg for rats, 389 mg/kg for mice and 381 mg/kg for guinea pigs.

- Drill and Hiratzka (1953) investigated the acute oral toxicity of 2,4,5-T in adult mongrel dogs given single oral doses of 50, 100, 250 or 400 mg/kg by gelatin capsule. Animals were observed for 14 days, at which time survivors were necropsied. The number of deaths at the four dose levels were 0/4, 1/4, 1/1 and 1/1, respectively. The LD_{50} value was estimated to be 100 mg/kg or higher. Marked changes were not observed in animals that died, effects being limited to weight loss, slight to moderate stiffness in the hind legs and ataxia (at the highest doses).

- Weanling male Wistar rats were fed diets containing 2,4,5-T for 3 weeks to investigate effects on the immune system (Vos et al., 1983). 2,4,5-T (>99% purity, TCDD content not specified) was fed at levels of 200, 1,000 or 2,500 ppm (approximately 20, 100 or 250 mg/kg/day, assuming 1 ppm equals 0.1 mg/kg/day in a younger rat by Lehman, 1959). Following the 3-week feeding period, the animals were sacrificed and the organs of the immune system, as well as other parameters of general toxicity, were examined. Even at the lowest dose level of 200 ppm in the diet, 2,4,5-T caused a significant ($p < 0.05$) decrease in relative kidney weight and a significant ($p < 0.05$) increase in serum IgG level, the most sensitive indicators of its effects. In this study, based on general toxicologic and specific immunologic effects in the rat, the Lowest-Observed-Adverse-Effect Level (LOAEL) was 20 mg/kg/day.

Dermal/Ocular Effects

- Gehring and Betso (1978) summarized the effects of 2,4,5-T on the skin and the eye. The dry material is slightly irritating to the skin and the eye. Highly concentrated solutions may burn the skin with prolonged or repeated contact and can strongly irritate the eye and possibly cause corneal damage. Preparations of 2,4,5-T formerly contained 1 to 80 ppm 2,3,7,8-TCDD, a concentration high enough to cause chloracne in industrial workers (NAS, 1977).

Long-term Exposure

- Drill and Hiratzka (1953) investigated the subchronic toxicity of 2,4,5-T in adult mongrel dogs. One or two dogs of each sex per group were fed capsules in food containing 0, 2, 5, 10 or 20 mg/kg 2,4,5-T, 5 days per week for 13 weeks. Animals were weighed twice weekly, and blood was taken on days 0, 30 and 90. Upon death or completion of the study, animals were necropsied with histological examination of a number of tissues. No deaths occurred at doses of 10 mg/kg/day or less, but 4/4 animals receiving 20 mg/kg/day died. No effects on body weight, hematology and pathology were seen except in animals that died. The No-Observed-Adverse-Effect Level (NOAEL) was identified as 10 mg/kg/day.

- McCollister and Kociba (1970) examined the effects of 2,4,5-T administered in the diet for 90 days to male and female Sprague-Dawley rats (Spartan strain). The 2,4,5-T (99.5% pure, <0.5 ppm dioxin) was included in the diet at levels corresponding to doses of 0, 3, 10, 30 or 100 mg/kg/day. Five animals of each sex were used at each dose level. At the conclusion of the study, necropsy, urinalyses, blood counts and clinical chemistry assays were performed. There was no mortality in any group. At 100 mg/kg, animals of both sexes had depressed ($p < 0.05$) body weight gain, a slight but significant ($p < 0.05$) decrease in food intake and elevated ($p < 0.05$) serum alkaline phosphatase (AP) levels. Necropsy revealed paleness and an accentuated lobular pattern of the liver, with some inconsistent hepatocellular swelling. Males (but not females) had slightly elevated serum glutamic-pyruvic transaminase (SGPT) levels, and slight decreases in red blood cell counts and in hemoglobin. Males given 100 mg/kg/day had increased ($p < 0.05$) kidney/body and liver/body weights. At the 30 mg/kg/day dose level, males exhibited increased ($p < 0.05$) liver/body and kidney/body weight ratios and kidney weights. Females given 30 mg/kg/day had slightly but significantly ($p < 0.05$) elevated AP and SGPT levels, but the authors felt that the clinical significance of these latter findings was doubtful. No treatment-related effects were observed at the 3 or 10 mg/kg dose level. From this study, a NOAEL of 10 mg/kg/day and a LOAEL of 30 mg/kg/day were identified.

- Groups of Sprague-Dawley rats (50/sex/level) were maintained on diets supplying 3, 10 or 30 mg/kg/day of 2,4,5-T for 2 years (Kociba et al., 1979). The 2,4,5-T was approximately 99% pure, containing 1.3% (w/w) other phenoxy acid impurities. Dioxins were not detected, the limit of detection for TCDD being 0.33 ppb. An interim sacrifice was performed on an additionally included group of 10 animals of each sex at 118 to 119 days. Control groups included 86 animals of each sex. The highest dose level was associated with some degree of toxicity, including a decrease in body weight gain ($p < 0.05$ in females) and an increase in relative kidney weight ($p < 0.05$ in males). Increases ($p < 0.05$) in the volume of urine excreted and in the urinary excretion of coproporphyrin and uroporphyrin were also observed at this dose level. Increased ($p < 0.05$) morphological changes were observed in the kidney, liver and lungs of animals administered 30 mg/kg/day. The kidney changes involved primarily the presence ($p < 0.05$) of mineralized deposits in the renal pelvis in females. Effects noted at the 10 mg/kg dose level were primarily an increased ($p < 0.05$) incidence of mineralized deposits in the renal pelvis in females. During the early phase of the study there was an increase ($p < 0.05$) in urinary excretion of coproporphyrin in males. At the lowest dose level (3 mg/kg), there were no changes that were considered to be related to treatment throughout the 2-year period. From this study in rats, a NOAEL of 3 mg/kg/day was identified.

Reproductive Effects

- Male and female Sprague-Dawley rats (F_0) were fed lab chow containing 2,4,5-T (<0.03 ppb TCDD) to provide dose levels of 0, 3, 10 or 30 mg/kg/day for 90 days and then were bred (Smith et al., 1981). At day 21 of lactation, pups were randomly selected for the following generation (F_1) and the rest were necropsied. Subsequent matings were conducted to produce F_2, F_{3a} and F_{3b} litters, successive generations being fed from weaning on the appropriate test or control diet. Fertility was decreased ($p < 0.05$) in the matings of the F_{3b} litters in the group given 10 mg/kg/day. Postnatal survival was significantly ($p < 0.05$) decreased in the F_2 litters of the 10 mg/kg group and in the F_1, F_2 and F_3 litters of the 30 mg/kg group. A significant decrease ($p < 0.05$) in relative thymus weight was seen only in the F_{3b} generation of the 30 mg/kg group, but the relative liver weights of weanlings was significantly ($p < 0.05$) increased in the F_2, F_{3a} and F_{3b} litters of this dosage group. Smith et al. (1981) concluded that dose levels of 2,4,5-T that were sufficiently high to cause signs of toxicity in neonates had no effect on the reproductive capacity of the rats, except for a tendency toward a reduction of postnatal survival at a dose of 30 mg/kg. Reproduction was not impaired at the lowest dose of 3 mg/kg. The apparent NOAEL with respect to reproductive capacity and fetotoxic effects in this study is 3 mg/kg/day, taking into consideration the report, on apparently the same study, by Smith et al. (1978) who noted a significant ($p < 0.05$) decrease in F_1 (10 and 30 mg/kg on days 14 and 21) and F_3 (3 mg/kg on day 14, and 10 and 30 mg/kg on day 21) litters and concluded that there was no effect of 2,4,5-T on rat reproduction except for a tendency toward a reduction in neonatal survival at 10 and 30 mg/kg.

Developmental Effects

- Sparschu et al. (1971) tested 2,4,5-T (commercial grade, 0.5 ppm TCDD) at levels of 50 or 100 mg/kg/day in pregnant rats (strain not specified) on either days 6 to 15 (50 mg/kg) or days 6 to 10 (100 mg/kg) of gestation. The 2,4,5-T was administered by oral intubation in a solution of Methocel, and controls were given an appropriate volume of Methocel. At the 50 mg/kg dose, there was a slightly higher incidence of delayed ossification of the skull bones, but this was not considered a teratogenic response. The 100 mg/kg dose (administered on days 6 to 10) was toxic to the dams and caused a high incidence of maternal deaths (only 4 of the 25 pregnant rats survived). Of these, three had complete early resorptions, and one had a litter of 13 viable fetuses that showed toxic effects (not further described) but no terata. From these data for maternal effects, a NOAEL of 50 mg/kg and a LOAEL of 100 mg/kg were identified. Also identified were a NOAEL of 100 mg/kg for teratogenicity and a LOAEL of 50 mg/kg for fetotoxicity.

- A sample of 2,4,5-T (technical grade) containing 0.5 ppm TCDD as well as other phenoxy compounds was administered to CD-1 rats by oral intubation on days 6 through 15 of gestation at dose levels of 10, 21.5, 46.4 or 80 mg/kg/day (Courtney and Moore, 1971). Examination of offspring revealed that the sample was not teratogenic at these dose levels. There was a significant ($p < 0.05$) increase in fetal mortality at the 80 mg/kg/day dose levels (the maternal LD_{40}). In two 2,4,5-T-treated fetuses, mild gastrointestinal hemorrhages were observed as a fetotoxic effect. Kidney anomalies were also slightly increased with the effect most pronounced at the 80 mg/kg level, but the number of litters examined was too small to evaluate this observation. In a separate study, rats were administered 50 mg/kg/day in an identical protocol, but in this case they were allowed to litter, and the neonates were examined and weighed on day 1 and followed for 21 days. Postnatal growth and development were comparable to that of the control animals. A NOAEL of 46.4 mg/kg/day for both fetotoxicity and teratogenicity in the CD-1 rat was identified from these data.

- Sprague-Dawley rats (50/group) and New Zealand White rabbits (20/group) were given oral doses (gavage for rats, capsules for rabbits) of 2,4,5-T (containing 0.5 ppm TCDD) during gestation (Emerson et al., 1971). The rats received daily doses of 1, 3, 6, 12 or 24 mg/kg on days 6 through 15, while the rabbits were administered 10, 20 or 40 mg/kg on days 6 through 18 of gestation. In both species, animals were observed daily, weighed periodically and subjected to Cesarean section prior to parturition. Rabbit pups were kept for observation for 24 hours and then sacrificed. There were no observable adverse effects in dams of either species treated with the 2,4,5-T. Litter size, number of fetal resorptions, birth weights and sex ratios all appeared to be unaffected in the treated groups. Detailed visceral and skeletal examinations were performed on the control and high-dose groups for each species, and no embryotoxic or teratogenic effects were revealed. A NOAEL for fetotoxic and maternal effects identified from this study was 24 mg/kg/day for the rat and 40 mg/kg/day for the rabbit.

- Several different samples of 2,4,5-T (containing <0.5 ppm TCDD) were tested in pregnant Wistar rats by daily oral administration on days 6 through 15 of gestation at dose levels between 25 and 150 mg/kg/day (Khera and McKinley, 1972). In some cases, fetuses were removed by Cesarean section for examination; some animals were allowed to litter, and the offspring were observed for up to 12 weeks. At doses of 100 mg/kg, there was an increase ($p < 0.05$) in fetal mortality and an increase ($p < 0.05$) in skeletal variations; a visceral anomaly was noted (dilatation of the renal pelvis), which was slightly increased over the control level, but was not statistically significant ($p > 0.05$). The survival of the progeny was not affected up to doses of 100 mg/kg, and in only one trial was there a low average litter size and viability.

This effect was not duplicated in a repeat test with the same sample. At the 25 and 50 mg/kg dose levels, significant ($p < 0.05$) differences from controls were not apparent. With respect to fetotoxicity, this study identified a NOAEL of 50 mg/kg/day in the rat.

- The teratogenic effects of 2,4,5-T were examined in golden Syrian hamsters after oral dosing (by gavage) on days 6 through 10 of gestation at dose levels of 20, 40, 80 or 100 mg/kg/day (Collins et al., 1971). Four samples of 2,4,5-T with dioxin levels of 45, 2.9, 0.5 or 0.1 ppm were administered. Three samples, which had no detectable dioxin (based on TCDD), were also tested. The 2,4,5-T samples induced fetal death and terata. The incidence of effects increased with increasing content of the TCDD impurity. 2,4,5-T with no detectable dioxin produced no malformations below the 100 mg/kg dose level. Using the data from the 2,4,5-T samples with no detectable dioxin, a NOAEL of 80 mg/kg/day for the hamster was identified.

- Behavioral effects resulting from in utero exposure to 2,4,5-T were examined in Long-Evans rats after single oral doses were administered during gestation (Crampton and Rogers, 1983). The sample of 2,4,5-T contained <0.03 ppm TCDD. Novelty response (latency, ambulation, rearing, grooming, and defecation in open field testing) abnormalities in offspring were detected after single doses as low as 6 mg/kg were administered on day 8 of gestation. Examination of the brain in the affected offspring failed to reveal any changes of a qualitative or quantitative structural nature in various areas of the brain. With respect to behavioral effects, the LOAEL for this study is 6 mg/kg.

- The teratogenic effects of technical 2,4,5-T (TCDD content 0.1 ppm) were studied using large numbers of pregnant mice of C57BL/6, C3H/He, BALB/c and A/JAX inbred strains and CD-1 stock (Gaines et al., 1975). Dose-response curves were determined for the incidence of cleft palate, embryo lethality and fetal growth retardation. These determinations were replicated 6 to 10 times for each inbred strain and 35 times for the CD-1. The number of litters studied ranged from 236 for BALB/c mice to 1,485 for CD-1 mice. Treatment was by gavage on days 6 to 14 of pregnancy, and dose levels of 2,4,5-T ranged from 15 to 120 mg/kg/day. The lowest dose tested in the A/JAX was 15 mg/kg, and this dose was teratogenic. The other strains and CD-1 demonstrated teratogenicity at 30 mg/kg, the lowest dose tested. There were significant ($p < 0.05$) differences in sensitivities among the strains for the parameters measured. Based on this study in the mouse, the LOAEL for teratogenic effects is 15 mg/kg/day for the A/JAX strain and 30 mg/kg/day for the other strains.

- Neubert and Dillmann (1972) studied the effects of 2,4,5-T in pregnant NMRI mice. Three samples of 2,4,5-T were utilized: one had <0.02 ppm dioxin, and was considered "dioxin-free"; a second sample had a dioxin content of 0.05 ± 0.02 ppm; and the third sample had an undetermined dioxin content. The 2,4,5-T was administered by gavage on days 6 through 15 of gestation at dose levels from 8 to 120 mg/kg/day. Fetuses were removed on day 18 and examined. Cleft palate frequency exceeding ($p < 0.05$) that of the controls was observed with doses higher than 30 mg/kg with all samples. Reductions ($p < 0.05$) in fetal weight were observed with all samples tested at doses as low as 10 to 15 mg/kg. There was no clear increase in embryo lethality over that of controls at these lower doses. With the purest sample of 2,4,5-T, single oral doses of 150 to 300 mg/kg were capable of producing significant ($p < 0.05$) incidences of cleft palate. The maximal teratogenic effect was seen when the 2,4,5-T was administered on days 12 to 13 of gestation. Based on the data obtained with the purest sample of 2,4,5-T, the teratogenic NOAEL is 15 mg/kg/day and the fetotoxic NOAEL is 8 mg/kg/day.

- Roll (1971) examined the teratogenic effects of 2,4,5-T in NMRI-Han mice after oral administration on days 6 to 15 of gestation at dose levels of 0, 20, 35, 60, 90 or 130 mg/kg/day. The 2,4,5-T sample had a purity of 99.6%, with a dioxin content of <0.01 ppm (measured by the DOW method), or 0.05 ± 0.02 ppm (measured by the U.S. Food and Drug Administration (FDA) method). Peanut oil was used as the vehicle. Animals were sacrificed on day 18 and examined for defects. Fetal weight was significantly ($p < 0.05$) lower than control at all doses. Resorptions were significantly ($p < 0.05$) increased at 60 mg/kg and above. The incidence of cleft palates was significantly ($p < 0.05$) higher at 35 mg/kg and higher, but there was no effect at 20 mg/kg. There were also dose-dependent increases in ossification defects of sternum and various other bones. The authors concluded that 2,4,5-T alone (independent of TCDD contamination) was teratogenic in mice, and that the teratogenic NOAEL in this strain was 20 mg/kg/day. In view of the significantly ($p < 0.05$) lower fetal weight at 20 mg/kg/day, this level may also be considered the LOAEL for fetotoxicity.

- No teratogenic effects were observed in the offspring of female rhesus monkeys that were given oral doses of 0.05, 1.0 or 10.0 mg 2,4,5-T (containing 0.05 ppm TCDD)/kg/day in capsules during gestation days 22 through 38. Neither was toxicity evident in the mothers (Dougherty et al., 1976).

Mutagenicity

- At 250 and 1,000 ppm 2,4,5-T (with no detectable TCDD), mutation rate was significantly ($p < 0.05$) increased at the higher dose in the sex-linked recessive lethal test in *Drosophila* as carried out by Majumdar and Golia (1974). The sex-linked test was not affected by 920 or 1,804 ppm of the sodium salt of 2,4,5-T at pH 6.8 in a study carried out by Vogel and Chandler (1974). Although they found no cytogenetic effects in *Drosophila*, Magnusson et al. (1977) concluded that 1,000 ppm 2,4,5-T (<0.1 ppm TCDD) did cause an increase ($p < 0.05$) in the number of recessive lethals compared to the controls. Rasmusson and Svahlin (1978) treated *Drosophila* larvae with food containing 100 and 200 ppm 2,4,5-T; survival was low at 200 ppm, but 2,4,5-T had no observable effect on somatic mutational activity.

- Anderson et al. (1972) found that neither 2,4,5-T nor its butyric acid form showed any mutagenic action when tested on histidine-requiring mutants of *Salmonella typhimurium*.

- Buselmaier et al. (1972) found that intraperitoneal injection of 2,4,5-T (dioxin levels not given) had no effect in the host-mediated assay (500 mg/kg) or in the dominant lethal test (100 mg/kg) with NMRI mice. Styles (1973), likewise, found no increase in back mutation rates with the serum of rats treated orally with 2,4,5-T in the host-mediated assay with _Salmonella typhimurium_ (dosages and purity of the samples not given).

- Shirasu et al. (1976) found that 2,4,5-T did not induce mitotic gene conversion in a diploid strain of _Saccharomyces cerevisiae_. When the pH of the treatment solution was less than 4.5, Zetterberg (1978) found that 2,4,5-T was mutagenic in haploid, DNA-repair-defective _S. cerevisiae_.

- Jenssen and Renberg (1976) investigated the cytogenetic effects of 2,4,5-T in mice by examining the ability of the herbicide to induce micronuclei formation in the erythrocytes of mouse bone marrow. CBA mice were treated at 8 to 10 weeks of age (20 to 30 g) with a single intraperitoneal injection of 100 mg/kg of 2,4,5-T (<1 ppm TCDD) dissolved in Tween 80 and physiological saline. Cytogenetic examination at 24 hours and 7 days after treatment showed no detectable increase in micronuclei in the erythrocytes compared to controls. A weak toxic effect on the mitotic activity was indicated, as judged by a decrease in the percentage of polychromatic erythrocytes.

Carcinogenicity

- Innes et al. (1969) investigated the potential carcinogenic effects of 2,4,5-T in two hybrid strains of mice derived by breeding SPF C57BL/6 female mice to either C3H/Anf or AKR males. Beginning at 6 days of age, 2,4,5-T was administered by gavage in 0.5% gelatin to a group of 72 mice at a dose level of 21.5 mg/kg/day. This was reported to be the maximum tolerated dose. At 28 days of age, the 2,4,5-T was added to the diet at a level of 60 ppm, corresponding to a dose of about 9 mg/kg/day (assuming that 1 ppm equals 0.15 mg/kg/day in the diet from Lehman, 1959). This dose was fed for 18 months, at which time the study was terminated. All animals were necropsied and the tissues were examined both grossly and microscopically. There were no significant ($p < 0.05$) increases in tumors in either strain of treated mice.

- A lifetime study using oral administration of 2,4,5-T in both sexes of two strains of mice, C3Hf and XVII/G, was performed by Muranyi-Kovacs et al. (1976). The 2,4,5-T, which contained less than 0.05 ppm of dioxins, was administered in the water (1,000 mg/L) for 2 months beginning at 6 weeks of age, and thereafter in the diet at 80 ppm (12 mg/kg/day) until death or when the mice were sacrificed _in extremis_. In the treated C3Hf mice there was a significant ($p < 0.03$) increase in the incidence of total tumors found in female mice and a significant ($p < 0.001$) increase in total nonincidental tumors in each sex, which the authors interpreted as life-threatening. No significant ($p < 0.05$) difference was found in the XVII/G strain between the treated and control mice. The authors felt that although 2,4,5-T demonstrated carcinogenic potential in the C3Hf strain, additional studies in other strains and in other species of animals needed to be performed before a reliable conclusion with respect to carcinogenicity could be made.

- Groups of Sprague-Dawley rats (50 males and 50 females) were maintained on diets supplying 3, 10 or 30 mg/kg/day of 2,4,5-T for 2 years (Kociba et al., 1979). The 2,4,5-T was approximately 99% pure, containing 1.3% (w/w) other phenoxy acid impurities. Dioxins were not detected, the limit of detection for TCDD being 0.33 ppb. An interim sacrifice was performed on an additionally included group of 10 animals of each sex at 118 to 119 days. Control groups included 86 animals of each sex. At the end of the 2-year period, there was no significant ($p > 0.05$) increase in tumor incidence in any treated group compared to the control for either male or female animals.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for 2,4,5-T. The study in humans by Gehring et al. (1973) was not selected because observations of the subjects were reported simply as clinical effects without further details. The behavioral study in rats by Crampton and Rogers (1983) was not selected because the interpretation of altered novelty response behavior in the absence of other toxic signs needs further investigation before definitive conclusions can be made. It is therefore recommended that the Ten-day HA value for a 10-kg child (0.8 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Neubert and Dillman (1972) has been selected to serve as the basis for determination of the Ten-day HA value for 2,4,5-T. This developmental study in rats identified a NOAEL of 8 mg/kg/day and a LOAEL of 15 mg/kg/day, based on reduced body weights in pups from dams exposed on days 6 to 15 of gestation. This LOAEL is supported by a number of other developmental studies in rodents that identified LOAELs ranging from 15 to 100 mg/kg/day (Roll, 1971; Sparschu et al., 1971; Khera and McKinley, 1972; Gaines et al., 1975). In the 21-day feeding study in rats by Vos et al. (1983), a LOAEL of 20 mg/kg/day was identified based on effects on kidney weight and the immune system. The 8 mg/kg/day NOAEL for fetal effects selected from the Neubert and Dillman (1972) study may not be applicable to a 10-kg child; however, the assumptions for a 10-kg child are used with this NOAEL in this case since, although a NOAEL was not found in the 21-day study by Vos et al. (1983) where the observed effects are applicable to a 10-kg child, the LOAEL of 20 mg/kg/day is 2.5 times higher than the NOAEL used for the Ten-day HA.

Using a NOAEL of 8 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(8\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.8\ \text{mg/L}\ (800\ \text{ug/L})$$

where:

8 mg/kg/day = NOAEL, based on absence of maternal or fetal effects in rats exposed by gavage on days 6 to 15 of gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The reproduction study by Smith et al. (1978, 1981) has been selected to serve as the basis for the Longer-term HA value for 2,4,5-T because the reduction in neonatal survival over multiple generations is concluded to be relevant to the Longer-term HA for a 10-kg child. The NOAEL identified was 3 mg/kg/day, and the LOAEL was 10 mg/kg/day. Other possible selections have a higher NOAEL [10 mg/kg/day in the 90-day feeding study in rats by McCollister and Kociba (1970) and the 90-day oral treatment study in dogs by Drill and Hiratzka (1953)].

Using a NOAEL of 3 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(3\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.3\ \text{mg/L}\ (300\ \text{ug/L})$$

where:

3 mg/kg/day = NOAEL, based on absence of adverse effects in neonatal rats in the three-generation reproduction study in rats given 2,4,5-T in the diet.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(3 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 1.05 \text{ mg/L } (1{,}000 \text{ ug/L})$$

where:

3 mg/kg/day = NOAEL, based on absence of adverse effects in neonatal rats in a three-generation reproduction study in rats given 2,4,5-T in the diet.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Kociba et al. (1979) has been selected to serve as the basis for the Lifetime HA value for 2,4,5-T. In this study, rats were fed 2,4,5-T in the diet for 2 years. Based on observations of effects of 2,4,5-T on various biochemical parameters in addition to gross and microscopic observations related to general toxicity in the rats, this study identified a NOAEL of 3 mg/kg/day and a LOAEL of 10 mg/kg/day. This study is supported by the three-generation rat study (Smith et al., 1981, 1978) that identified a NOAEL of 3 mg/kg/day.

Using this study, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(3.0 \text{ mg/kg/day})}{(100)\ (3)} = 0.01 \text{ mg/kg/day}$$

where:

3.0 mg/kg/day = NOAEL, based on absence of adverse effects on the kidneys, liver and lungs of rats exposed to 2,4,5-T in the diet for 2 years.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = modifying factor used by U.S. EPA Office of Pesticide Programs to account for data gaps (chronic feeding study in dogs) which does not make it possible to establish the most sensitive end point for 2,4,5-T.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.01 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.35 \text{ mg/L } (400 \text{ ug/L})$$

where:

0.01 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.35 \text{ mg/L})\ (20\%) = 0.07 \text{ mg/L } (70 \text{ ug/L})$$

where:

0.35 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Chronic feeding studies with 2,4,5-T in Sprague-Dawley rats (Kociba et al., 1979) and C57BL/6 x C3H/Anf, C57BL/6 x AKR and XVII/G strains of mice (Innes et al., 1969; Muranyi-Kovacs, et al; 1976) were negative for carcinogenic effects. A chronic feeding study with 2,4,5-T in C3Hf mice was inconclusive (Muranyi-Kovacs et al., 1976).

- IARC (1982) concluded that the carcinogenicity of 2,4,5-T is indeterminant (Group 3, inadequate evidence in animals and humans).

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), 2,4,5-T may be classified in Group D: not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

- The Carcinogen Assessment Group (CAG) of the U.S. EPA classified chlorophenoxyacetic acids and/or chlorophenols containing 2,3,7,8-TCDD in IARC category 2A (probably carcinogenic in humans on the basis of limited evidence in humans), but a quantitative cancer risk estimate only for 2,3,7,8-TCDD itself was made. The CAG considered the human evidence for the carcinogenicity of 2,3,7,8-TCDD alone to be "inadequate" because of the difficulty in attributing observed effects solely to the presence of 2,3,7,8-TCDD, which occurs as an impurity in the phenoxyacetic acids and chlorophenols (U.S. EPA, 1985).

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA/Office of Pesticide Programs has calculated a Provisional Acceptable Daily Intake (PADI) value of 0.003 mg/kg/day, based on the results of a rat chronic oral NOAEL of 3 mg/kg/day with an uncertainty factor of 300 (used because of a data gap).

- The National Academy of Sciences (NAS, 1977) has calculated an ADI of 0.1 mg/kg/day, using a NOAEL of 10 mg/kg/day (identified in a 90-day feeding study in dogs) and an uncertainty factor of 100. A chronic Suggested-No-Adverse-Effect-Level (SNARL) of 0.7 mg/L was calculated based on the ADI of 0.1 mg/kg/day.

- The American Conference of Governmental Industrial Hygienists (ACGIH, 1981) has recommended a Threshold Limit Value-Time-Weighted Average (TLV-TWA) of 10 mg/m^3 and a Threshold Limit Value-Short-Term Exposure Limit (TLV-STEL) of 20 mg/m^3.

- The ADI recommended by the World Health Organization is 0 to 0.03 mg/kg (Vettorazzi and van den Hurk, 1983).

VII. ANALYTICAL METHODS

- Determination of 2,4,5-T is by a liquid-liquid extraction gas chromatographic procedure (U.S. EPA, 1978; Standard Methods, 1985).

Specifically, the procedure involves the extraction of chlorophenoxy acids and their esters from an acidified water sample with ethyl ether. The esters are hydrolyzed to acids and extraneous organic material is removed by a solvent wash. The acids are converted to methyl esters which are extracted from the aqueous phase. Separation and identification of the esters is made by gas chromatography. Detection and measurement is accomplished by an electron capture, mcirocoulometric or electrolytic conductivity detector. Identification may be corroborated through the use of two unlike columns. The detection limit is dependent on the sample size and instrumentation used. Typically, using a 1 L sample and a gas chromatograph with an electron capture detector results in an approximate detection limit of 10 ng/L for 2,4,5-T.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) and powdered-activated carbon (PAC) adsorption will effectively remove 2,4,5-T from water.

- Robeck et al. (1965) experimentally determined adsorption isotherms for the butoxy ethanol ester of 2,4,5-T on PAC. Based on these results, it was calculated that 14 mg/L PAC would be required to remove 90% of 2,4,5-T, while 44 mg/L PAC would be required to remove 99% of 2,4,5-T (Pershe and Goss, 1979; Robeck et al., 1965).

- Robeck et al. (1965) reported the results of a GAC column operating under pilot plant conditions. At a flow rate of 0.5 gpm/ft^3, 99+% of 2,4,5-T was removed. By comparison, treatment with 5 to 20 mg/L PAC removed 80 to 95% of the same concentration of 2,4,5-T.

- In a laboratory study conducted with an exchange resin, Rees and Au (1979) reported 89±2% removal efficiency of 2,4,5-T from contaminated water by adsorption onto synthetic resins.

- Conventional water treatment technique of coagulation with alum, sedimentation and sand filtration removed 63% of the 2,4,5-T ester present in spiked river water (Robeck et al., 1965).

- Treatment technologies for the removal of 2,4,5-T from water are available and have been reported to be effective. However, selection of individual or combinations of technologies to attempt 2,4,5-T removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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August, 1988

TEBUTHIURON

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

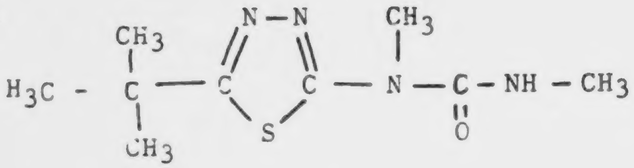
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 34014-18-1

Structural Formula



N-[5-(1,1-Dimethyl ethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea

Synonyms

- Combine; Herbic; Graslan; Perflan; Spike.

Uses

- Herbicide for total vegetation woody plant control in noncropland areas and for brush and weed control in rangeland (Meister, 1983).

Properties (Meister, 1983)

Chemical Formula	$C_9H_{16}ON_4S$
Molecular Weight	228 (calculated)
Physical State (25°C)	White crystalline, odorless powder; colorless solid
Boiling Point	--
Melting Point	159 to 161°C
Density	--
Vapor Pressure (25°C)	2×10^{-6} mm Hg
Specific Gravity	--
Water Solubility (25°C, pH 7)	2,500 mg/L
Log Octanol/Water Partition Coefficient	1.79
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- No occurrence data has been found in the STORET database (STORET, 1988).

Environmental Fate

- Tebuthiuron is resistant to hydrolysis. ^{14}C-Tebuthiuron, at 10 and 100 ppm, did not degrade during 64 days of incubation in sterile aqueous solutions at pH 3, 6 and 9 in the dark at 25°C (Mosier and Saunders, 1976).

- After 23 days of irradiation with artificial light (20-W black light), tebuthiuron accounted for 87 to 89% of the applied radioactivity in deionized (pH 7.1) and natural (pH 8.1) water treated with thiadiazole ring-labeled ^{14}C-tebuthiuron at 25 ppm (Elanco Products Company, 1972; Rainey and Magnussen, 1976b). After 15 days of irradiation with a black light or a sunlamp, tebuthiuron accounted for approximately 82 and 53%, respectively, of the applied compound in natural water treated with ^{14}C-tebuthiuron at 2.5 ppm.

- Thiadiazole ring-labeled ^{14}C-tebuthiuron in loam soil degraded from 8 ppm immediately post-treatment to 5.7 ppm at 273 days posttreatment indicating a half-life greater than 273 days (Rainey and Magnussen, 1976a, 1978).

- ^{14}C-Tebuthiuron, at 1.0 ppm, degraded with a half-life of greater than 48 weeks in a loam soil maintained under anaerobic conditions in the dark at 23°C (Berard, 1977). N-[5-(1,1-Dimethylethyl)-1,3,4-thiadiazol-2-yl]-N-methylurea was the major degradate.

- Ring-labeled ^{14}C-tebuthiuron was very mobile (>94% of that applied was found in the leachate) in a 12-inch column of Lakeland fine sand soil leached with 20 inches of water (Holzer et al., 1972). It was mobile in columns of loamy sand (approximately 73% at 6 to 10 inches), loam (approximately 84% at 1 to 8 inches) and muck (100% at 0 to 4 inches) soils leached with 4 to 8 inches of water.

- Based on column leaching studies, tebuthiuron is mobile to very mobile in loam, loamy sand, and Lakeland sand soils and has low mobility in silty loam soil (Day, 1976a).

- ^{14}C-Tebuthiuron residues aged 30 days were mobile in a column of sandy loam soil; 39% of ^{14}C-residues were found in the soil and 40% of ^{14}C-residues were in the leachate (Day, 1976b).

- ^{14}C-Tebuthiuron degraded with half-lives of greater than 33 months in field plots in California (loam soil), 12 to 15 months in Louisiana (clay soil), and 12 to 15 months in Indiana (loam soil). The three sites were treated with thiadiazole ring-labeled ^{14}C-tebuthiuron at 8.96, 2.24 and 8.96 kg/ha, respectively (Rainey and Magnussen, 1976a, 1978). N-[5-(1,1-Dimethylethyl)-1,3,4-thiadiazol-2-yl]-N-methylurea was the major degradate at all three sites. Radioactivity was detected in the 15- to 30-cm depth of soil (10.2% of the applied compound at 18 months) at the California site, in the 30- to 45-cm depth of soil (1.3% of the applied compound at 33 months) at the Louisiana site, and in the 30- to 45-cm depth of soil (4.7% of the applied compound at 15 months) at the Indiana site. ^{14}C-Tebuthiuron residues did not appear to accumulate in silt loam soil in Louisiana after three applications of ^{14}C-tebuthiuron (0.84 kg/ha at zero time; 1.4 kg/ha at 22 and 73 weeks).

III. PHARMACOKINETICS

Absorption

° Morton and Hoffman (1976) reported that 94 to 96% of a single oral dose of tebuthiuron (10 mg/kg) was excreted in the urine of rats, rabbits and dogs. In mice, 66% was excreted in the urine, and 30% in the feces. These data indicate that tebuthiuron was well absorbed (about 70 to 96%) from the gastrointestinal tract.

Distribution

° No quantitative data were found in the available literature on the tissue distribution of tebuthiuron in exposed animals.

° Adams et al. (1982) administered tebuthiuron in the diet to 20 pregnant Wistar rats at levels of 100 or 200 ppm for 6 days prior to delivery. Forty-eight hours after delivery, radiolabeled tebuthiuron was reintroduced into the diet at the same levels as before. Radioactive label was detected in the milk at mean levels of 2.7 and 6.2 ppm for the 100- and 200-ppm groups, respectively.

Metabolism

° Morton and Hoffman (1976) reported that tebuthiuron was metabolized extensively by mice, rats, rabbits and dogs. Tebuthiuron was administered by gavage to male and female ICR mice, Harlan rats, Dutch-Belted rabbits and beagle dogs at a dose of 10 mg/kg. Examination of urine extracts by thin-layer chromatography (TLC) showed the presence of eight radioactively labeled metabolites in rat, rabbit and dog urine and seven in mouse urine. Small amounts of unchanged tebuthiuron also were detected in each case (except for the mouse). The major metabolites were formed by N-demethylation of the substituted urea side-chain in each species examined. Oxidation of the dimethylethyl group also occurred in all species examined.

Excretion

° Morton and Hoffman (1976) reported that tebuthiuron was excreted rapidly in the urine of several species. Radiolabeled tebuthiuron was administered to male and female ICR mice, Harlan rats, Dutch-Belted rabbits and beagle dogs at a dose of 10 mg/kg by gavage. Elimination of radioactivity was virtually complete within 72 hours and recovery values at 96 hours were 96.3, 94.5, 94.3 and 95.7% in the mouse, rat, rabbit and dog, respectively. In the rats, rabbits and dogs, the radioactivity was excreted almost exclusively in the urine. In the mice, 30% of the radioactivity was excreted in the feces.

IV. HEALTH EFFECTS

Humans

- No information on the health effects of tebuthiuron in humans was found in the available literature.

Animals

Short-term Exposure

- Todd et al. (1974) reported the acute oral LD_{50} values of tebuthiuron in rats, mice and rabbits to be 644, 579 and 286 mg/kg, respectively. In cats, oral doses of 200 mg/kg were not lethal, while 500 mg/kg given orally was not lethal to dogs, quail, ducks or chickens.

- Todd et al. (1972a) supplied 40 weanling Sprague-Dawley rats (105-146g) with food containing tebuthiuron (purity not stated) at levels of 2,500 ppm for 15 days. At various time periods, 5 rats were necropsied and evaluated. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of a rat is equivalent to 0.05 mg/kg/day; therefore, this level corresponds to 125 mg/kg/day. The animals were observed for an additional 15-day recovery period. All the animals exhibited reduced body weight gain during the treatment period. Light and electron microscopic evaluation revealed formation of vacuoles containing electron-dense bodies and myeloid figures in pancreatic acinar cells. This condition was rapidly reversed during the recovery period.

Dermal/Ocular Effects

- Todd et al. (1974) administered 200 mg/kg tebuthiuron to the shaved, abraded backs of male and female New Zealand White rabbits. During the study, one rabbit died following development of diarrhea and emaciation. All surviving rabbits gained weight over the 14-day observation period and were without signs of dermal irritation.

- Todd et al. (1974) tested tebuthiuron for sensitization in 2- to 3-month-old female albino guinea pigs. Each animal received topical applications of 0.1 mL of an ethanolic solution containing 2% tebuthiuron to the region of the flank three times per week for 3 weeks. Ten days after the last of the nine treatments, a challenge application was made, followed by a second challenge 15 days after the first. Tebuthiuron induced no dermal or systemic responses indicative of contact sensitization.

- Todd et al. (1974) instilled 0.1 mL (71 mg) of tebuthiuron into one eye and conjunctival sac of each of six New Zealand White rabbits (2- to 3-months old). No irritation of the cornea or iris was observed, but there was slight transient hyperemia of the conjunctiva. All eyes were normal by the end of the 7-day test period.

Long-term Exposure

- Todd et al. (1972b) administered tebuthiuron (purity not stated) in the diet to groups of male and female Harlan rats (10/sex/group, 28- to 35-days old, 74 to 156 g) at levels of 0, 40, 100 or 250 mg/kg/day for 3 months. Body weights and food consumption were measured weekly. Blood obtained prior to necropsy was evaluated for blood sugar, blood urea nitrogen (BUN) and serum glutamic-pyruvic transaminase (SGPT). Sections of organs and tissues were prepared for gross and microscopic evaluation. There were no clinical signs of toxicity or mortality in any of the groups. A moderate reduction in body weight gain and a decrease in efficiency of food utilization in males and females in the highest dose group (250 mg/kg/day) was evident from week 1 of the study. Tebuthiuron had no clinically important effects on any of the hematological or clinical chemistry parameters measured. All rats receiving 250 mg/kg/day tebuthiuron showed diffuse vacuolation of the pancreatic acinar cells. The degree of this change ranged from slight to moderate, but the effect was not associated with necrosis or with the presence of an inflammatory response. One female rat receiving 100 mg/kg/day tebuthiuron showed very slight pancreatic changes. Based on these results, a No-Observed-Adverse-Effect-Level (NOAEL) of 40 mg/kg/day and a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 100 mg/kg/day were identified.

- Todd et al. (1972c) administered tebuthiuron (purity not stated) in gelatin capsules to groups of four beagle dogs (two/sex/group, 13- to 23-months old, 7 to 23 kg) at dose levels of 0, 12.5, 25 or 50 mg/kg/day for 3 months. The physical condition of the animals was assessed daily, and body weights were recorded weekly. Gross and microscopic histopathology examinations were performed. Anorexia was noted, especially in the high-dose animals, leading to some weight loss. There was no mortality. Behavior and appearance were unremarkable at all test levels. No abnormalities were seen in the hematological or urinalysis studies. Clinical chemistry findings indicated increased BUN in the 50-mg/kg females. In addition, this group and the 50-mg/kg males exhibited increasing levels of alkaline phosphatase, up to four-fold over those of controls; however, these levels had returned to normal at the terminal sampling. There were no urinary abnormalities. The 25-mg/kg females and males demonstrated increased thyroid-to-body weight ratios, and the 50-mg/kg females also showed increased spleen-to-body weight ratios. Histopathological findings were unremarkable. The LOAEL was identified as 25 mg/kg, based on increased thyroid-to-body weight ratios and increased alkaline phosphatase values. A NOAEL of 12.5 mg/kg was identified.

- Todd et al. (1976a) administered tebuthiuron (purity > 97%) in the diet to groups of Harlan rats (40/sex/dose) for 2 years at dietary levels of 0, 400, 800 or 1,600 ppm. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of a rat is equivalent to 0.05 mg/kg/day; therefore, these doses correspond to 20, 40 or 80 mg/kg/day. Physical appearance, behavior, food intake, body weight gain and mortality were recorded. Hematologic and blood chemistry values were obtained throughout the study; urinalysis was also performed. At necropsy, organ weights were determined and organs and tissues were examined grossly and histologically. Mortality in exposed animals was similar to, or less than, that observed in the control group. Variations in hematology, blood chemistry and urinalysis data from all groups were slight and unrelated to the test compound. Reduced body weight gain (10% or greater) was observed in the highest dose group animals. There was also a slight increase in the kidney weights of the high-dose males. Microscopic examination revealed a low incidence of slight vacuolation of the pancreatic acinar cells in animals in the highest dose group. The NOAEL for this study, based on acinar vacuolation, was 40 mg/kg.

° Todd et al. (1976b) administered tebuthiuron (purity not stated) in the diet for 2 years to groups of Harlan ICR mice (40/sex/dose) at levels of 0, 400, 800 or 1,600 ppm. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of a mouse is equivalent to 0.150 mg/kg/day; therefore, these dietary levels correspond to approximately 60, 120 or 240 mg/kg/day. Physical appearance, behavior, appetite, body weight gain and mortality were recorded. Hematologic, blood chemistry and organ weight values were obtained for animals surviving the test period. Gross and microscopic evaluations were conducted on organs and tissues obtained at necropsy. No important differences were observed between treated and control groups for any of the parameters evaluated. The vacuolation of pancreatic acinar cells noted in the Todd (1976a) rat studies was not evident in this study in mice. Based on this, the NOAEL for this study was identified as 240 mg/kg/day.

Reproductive Effects

° Hoyt et al. (1981) studied the effects of tebuthiuron (98% active ingredient) in a two-generation reproduction study in rats. Weanling Wistar rats (25/sex/dose, F_0 generation) were maintained on diets containing tebuthiuron at 0, 100, 200, and 400 ppm based on the active ingredient (0, 7, 14 or 28 mg/kg/day, based on actual food consumption) for a period of 101 days preceding two breeding trials. First generation (F_1) offspring were maintained on the same diets for a period of 124 days preceding two breeding trials. Spermatogenesis and sperm morphology were examined in 10 F_0 males per treatment group. In addition, representative F_{1a} and F_{2a} weanlings and F_1 adults were necropsied and given histopathologic examinations after live-phase observations were completed. No changes in the efficiency of food utilization (EFU) were noted during the F_0 growth period, but during the F_1 growth period, a statistically significant ($p \leq 0.05$) depression in cumulative (124 days) EFU values occurred in both male and female rats receiving 28 mg/kg/day. EFU was not affected at the other dose levels. A dose-related depression in mean body weight occurred among female rats of the F_1 generation receiving 14 or 28 mg/kg/day; mean body weight was depressed significantly ($p \leq 0.05$) only in the high-dose females. In the 7 mg/kg/day group, body weights of either sex were not affected. The reproductive capacity of the animals was not affected at any level; no dose-related conditions or lesions were found in any offspring. In adult males from the F_0 generation, no dose-related histologic lesions were found, and sperm morphology and spermatogenesis were normal. A LOAEL of 14 mg/kg/day was determined for a lower rate of body weight gain during the 101-day pre-mating period in F_1 females, and a NOAEL of 7 mg/kg/day, the lowest dose tested, was identified.

Developmental Effects

- Todd et al. (1972d) administered tebuthiuron (purity not stated) in the diet to groups of 25 adult Wistar-derived female rats (245 to 454 g) at levels of 0, 600, 1,200 or 1,800 ppm based on the active ingredient (0, 30, 60 or 90 mg/kg/day, based on Lehman, 1959) on days 6 to 15 of gestation. Fetal and uterine parameters were normal and the fetal defects that occurred were not attributed to the test compound. The NOAEL for developmental effects was greater than 1,800 ppm, the highest dose tested.

- Todd et al. (1975) administered tebuthiuron (purity not stated) by gavage to groups of 15 adult female Dutch-Belted rabbits at levels of 10 or 25 mg/kg/day on days 6 to 18 of gestation. No developmental or toxic effects were observed.

Mutagenicity

- Hill (1984) reported that primary cultures of adult rat hepatocytes incubated with concentrations of tebuthiuron ranging from 0.5 to 1,000 ug/mL did not exhibit unscheduled DNA synthesis.

- Rexroat (1984) reported that tebuthiuron did not induce Salmonella revertants (strains TA1535, 1537, 1538, 98 and 100) when tested at concentrations ranging between 100 and 5,000 ug/plate, with or without metabolic activation. It was concluded that tebuthiuron was not mutagenic in the Ames Salmonella/mammalian microsome test for bacterial mutation.

- Neal (1984) reported that tebuthiuron did not induce sister chromatid exchange in vivo in bone marrow cells of Chinese hamsters administered oral doses of 200, 300, 400 or 500 mg/kg tebuthiuron.

- Cline et al. (1978) reported that histadine auxotrophs of Salmonella typhimurium (strains G46, TA1535, 100, 1537, 1538, 98, C3076 and D3052) and tryptophan auxotrophs of Escherichia coli were not reverted to the prototype by tebuthiuron at levels of 0.1 to 1,000 ug/mL, with or without metabolic activation.

Carcinogenicity

- Todd et al. (1976a) administered tebuthiuron (purity > 97%) in the diet to groups of Harlan rats (40/sex/dose) at levels of 0, 400, 800 or 1,600 ppm based on the active ingredient (0, 20, 40 or 80 mg/kg/day, based on Lehman, 1959) for 2 years. The authors reported no influence of the test compound on the incidence of neoplasms at any dose level.

- Todd et al. (1976b) administered tebuthiuron in the diet to groups of Harlan ICR mice (40/sex/dose) at levels of 0, 400, 800 or 1,600 ppm (0, 60, 120 or 240 mg/kg/day, based on Lehman, 1959) for 2 years. The authors reported no statistical evidence of increased incidence of tumors at any dose level.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for the determination of the One-day HA value for tebuthiuron. It is therefore recommended that the Ten-day value for a 10-kg child, 2.5 mg/L (3,000 ug/L, calculated below), be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Todd et al. (1975) has been selected to serve as the basis for the Ten-day HA value for tebuthiuron because the NOAEL in the Dutch-Belted rabbit was the lowest end point observed in a short-term developmental study. This study identified a NOAEL of 25 mg/kg/day (the highest dose tested) based on an absence of maternal toxicity. In another developmental study in rats by Todd et al. (1972d), a NOAEL of 90 mg/kg/day (the highest dose tested) was recorded. Since it is unknown whether the rabbit or the rat is more sensitive, the lower NOAEL was conservatively chosen in deriving the 10-day HA.

Using a NOAEL of 25 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(25\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 2.5\ \text{mg/L}\ (3{,}000\ \text{ug/L})$$

where:

25 mg/kg/day = NOAEL, based on the absence of maternal toxicity in Dutch-Belted rabbits exposed to tebuthiuron by diet.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisories

The two-generation reproduction study in rats (Hoyt et al., 1981) has been chosen to serve as the basis for the Longer-term HA for tebuthiuron. In this study, four groups of Wistar rats (25/sex) were fed tebuthiuron at 0, 7, 14, and 28 mg/kg/day in the diet for 101 days (F_0 rats) or 121 days (F_1 rats) and then for a further period sufficient to mate, deliver, and rear two successive litters of young to 21 days of age. No adverse effects were reported in this study except for a lower body weight gain during premating period in F_1 females at the dietary levels of 14 and 28 mg/kg. The NOAEL was identified as 7 mg/kg/day. The chronic study by Todd et al. (1976b) in mice was not selected because the weight loss and vacuolization of pancreatic acinar cells noted in rats was not observed in mice even at dose levels as high as 160 mg/kg/day, indicating that the mouse is less sensitive than the rat. The subchronic (90-day) feeding study in beagle dogs reported by Todd et al. (1972) was not selected because the NOAEL (12.5 mg/kg/day) identified in that study was significantly higher than that of the rat study. In addition, the duration of the rat study was more appropriate for the derivation of a Longer-term HA.

Using the NOAEL of 7 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(7\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ \ (1\ \text{L/day})} = 0.7\ \text{mg/L}\ (700\ \text{ug/L})$$

where:

7 mg/kg/day = NOAEL, based on effects on the rate of weight gain in rats exposed to tebuthiuron in the diet for 101 days.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(7\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 2.45\ \text{mg/L}\ (2000\ \text{ug/L})$$

where:

7.0 mg/kg/day = NOAEL, based on effects on the rate of weight gain in rats exposed to tebuthiuron in the diet for 101 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The two-generation reproduction study in rats (Hoyt et al., 1981) has been selected to serve as the basis for the Lifetime HA value for tebuthiuron. In this study, four groups of Wistar rats (25/sex) were fed tebuthiuron at 0, 7, 14 or 28 mg/kg/day in the diet for 101 days (F_0 rats) or 121 days (F_1 rats) and then for a further period sufficient to mate, deliver and rear two successive litters of young to 21 days of age (i.e., the test diet was fed throughout mating, gestation and lactation). The F_{1a} rats were parents of the F_2 offspring. No adverse effects were reported in this study except for a lower rate of body weight gain during the premating period in F_1 females at dietary levels of 14 and 28 mg/kg. The NOAEL was identified as 7 mg/kg/day. The chronic study by Todd et al. (1976b) in mice was not selected because the weight loss and vacuolation of pancreatic acinar cells noted in rats was not observed in mice even at dose levels as high as 160 mg/kg/day, indicating that the mouse is less sensitive than the rat.

Using the NOAEL of 7 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(7\ \text{mg/kg/day})}{(100)} = 0.07\ \text{mg/kg/day}$$

where:

7 mg/kg/day = NOAEL, based on effects on the rate of weight gain in rats exposed to tebuthiuron in the diet for 101 days.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.07\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 2.45\ \text{mg/L}\quad (2{,}000\ \text{ug/L})$$

where:

0.07 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (2.45\ \text{mg/L})\ (20\%) = 0.49\ \text{mg/L}\ (500\ \text{ug/L})$$

where:

2.45 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of tebuthiuron.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), tebuthiuron may be classified in Group D: not classifiable as to human carcinogenicity. This category is for substances with inadequate human and animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

° No other criteria, guidance or standards were found in the available literature.

VII. ANALYTICAL METHODS

° Analysis of tebuthiuron is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus-containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. This method has been validated in a single laboratory, and estimated detection limit for the analytes in the method, such as tebuthiuron, is 1.3 ug/L.

VIII. TREATMENT TECHNOLOGIES

° No information on treatment technologies capable of effectively removing tebuthiuron from contaminated water was found in the available literature.

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*Confidential Business Information submitted to the Office of Pesticide Programs

August, 1988

TERBACIL

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

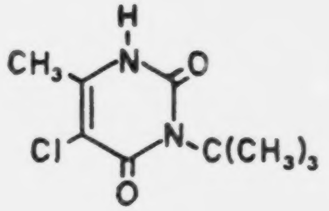
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 5902-51-2

Structural Formula



5-Chloro-3-(1,1-dimethylethyl)-6-methyl-2,4(1H,3H)-pyrimidinedione or 3-tert-Butyl-5-chloro-6-methyluracil

Synonyms

- Sinbar; Geonter (Meister, 1988).

Uses

- Herbicide used for the selective control of annual and perennial weeds in crops such as sugarcane, alfalfa, apples, peaches, blueberries, strawberries, citrus, pecans and mint (Meister, 1988).

Properties (Meister, 1988)

Chemical Formula	$C_9H_{13}O_2N_2Cl$
Molecular Weight	216.65
Physical State (at 25°C)	White crystals
Boiling Point (at 25 mm Hg)	--
Melting Point	175-177°C
Density	1.34 g/mL (25°C)
Vapor Pressure (29.5°C)	4.8×10^{-7} mm Hg
Specific Gravity	1.34 (25/25°C)
Water Solubility (25°C)	710 mg/L
Log Octanol/Water Partition Coefficient	-1.41
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Terbacil was not sampled at any water supply stations listed in the STORET database (STORET, 1988). No information was found in available literature on the occurrence of terbacil.

Environmental Fate

- ^{14}C-Terbacil at 5 ppm was stable (less than 2% degraded) in buffered aqueous solutions at pH 5, 7, and 9 for 6 weeks at 15°C in the dark (Davidson et al. 1978).

- After 4 weeks of irradiation with UV light (300 to 400 nm), about 16% of the applied ^{14}C-terbacil (5 ppm) was photodegraded in distilled water (pH 6.2) (Davidson et al., 1978).

- Soil metabolism studies indicate that terbacil is persistent in soil. At 100 ppm, terbacil was slowly degraded in an aerobic sandy loam soil (80% remained after 8 months) (Marsh and Davies, 1978). Terbacil at 8 ppm had a half-life of about 5 months in aerobic loam soil (Zimdahl et al., 1970). ^{14}C-Terbacil at 2 ppm had a half-life of 2 to 3 months in aerobic silt loam and sandy loam soils (Rhodes, 1975; Gardiner, 1964; Gardiner et al., 1969). The formation of carbon dioxide is slow; for example, 28% of the applied ^{14}C-terbacil at 2.88 ppm on sandy loam soil degraded to carbon dioxide in 600 days (Wolf, 1973; Wolf, 1974; Wolf and Martin, 1974).

- Degradation of terbacil in an anaerobic soil environment is also slow. In anaerobic silt loam and sandy soils, ^{14}C-terbacil at 2.1 ppm was slightly degraded (less than 5% after 60 days) in the dark (Rhodes, 1975). Only trace amounts of ^{14}C-terbacil, applied at 2.88 ppm, were degraded to ^{14}C-carbon dioxide after 145 days in an anaerobic environment when metabolized by microbes in the dark (Rhodes, 1975). At least 90% of the label remained as terbacil after 90 days of incubation in both sterile and nonsterile soils. Small amounts (0.8 to 1.5% of the label of carbon dioxide were evolved from nonsterile soil, whereas 0.01% was evolved from sterile soil (Rhodes, 1975).

- Terbacil was mobile in soil columns of sandy loam and fine sandy soil (Rhodes, 1975; Mansell et al., 1972). However, in a silt loam soil column, only 0.4% of the applied ^{14}C-terbacil leached with 20 inches of water (Rhodes, 1975). In an aged soil column leaching study of the leaching characteristics of degradates, about 52% and 4% of the applied radioactivity in aged sandy loam and silt loam soils leached, respectively (Rhodes, 1975). Terbacil phytotoxic residues were mobile to depths of 27.5 to 30 cm in a sandy soil column treated with terbacil at 5.6 kg/ha and eluted with 10 or 20 cm water (Marriage, 1977). Terbacil was negligibly adsorbed to soils ranging in texture from sand to clay (Davidson et al., 1978; Liu et al., 1971; Rao and Davison, 1979). Terbacil was adsorbed (54%) to a muck soil (36% organic matter) (Liu et al., 1971).

- Data from field dissipation studies showed that terbacil persistence in soil varied with application rate, soil type and rainfall. In the field, terbacil phytotoxic residues persisted in soil for up to 16 months following a single application of terbacil. Residues were found at the maximum depths sampled (3 to 43 inches) (Gardiner, undated a,b; Gardiner et al., 1969; Isom et al., 1969; Isom et al., 1970; Liu et al., undated; Mansell et al., 1977; Mansell et al., 1979; Morrow and McCarty, 1976; Rahman, 1977; Rhodes, 1975).

- Phytotoxic residues resulting from multiple applications of terbacil persisted for 1 to more than 2 years following the final application (Skroch et al., 1971; Tucker and Phillips, 1970; Benson, 1973; Doughty, 1978).

- Terbacil has not been found in ground water; however, its soil persistence and mobility indicate that it has the potential to get into ground water.

III. PHARMACOKINETICS

Absorption

- No information was found in the available literature on the absorption of terbacil. However, evidence of systemic toxicity indicates that terbacil is absorbed following ingestion.

Distribution

- No information was found in the available literature on the distribution of terbacil.

Metabolism

- No information was found in the available literature on the metabolism of terbacil.

Excretion

- No information was found in the available literature on the excretion of terbacil.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of terbacil in humans.

Animals

Short-term Exposure

- It was not possible to determine a lethal dose of terbacil in dogs because repeated emesis prevented dosing with terbacil in amounts in excess of 5,000 mg/kg (Paynter, 1966). However, in a dog receiving one oral dose of terbacil at 250 mg/kg followed 5 days later by a dose of 100 mg/kg, emesis, diarrhea and mydriasis were noted.

- In rats (details not available), the LD_{50} was between 5,000 and 7,500 mg/kg (Sherman, 1965). At 2,250 mg/kg, inactivity, weight loss and incoordination were noted.

Dermal/Ocular Effects

- Hood (1966) reported that no compound-related clinical or pathological changes were observed when terbacil was applied to the clipped dorsal skin of rabbits (five males, five females) at a dose level of 5,000 mg/kg (as a 55% aqueous paste), for 5 hours/day, 5 days/week for 3 weeks (15 applications). The parameters observed included body weight, dermal reaction, organ weights and histopathology.

- Reinke (1965) reported that no dermal reactions were observed when terbacil was administered to the intact dorsal skin of 10 guinea pigs as a 15% solution in 1:1 acetone:dioxane containing 13% guinea pig fat.

- Reinke (1965) reported no observed sensitization in ten albino guinea pigs when terbacil was administered nine times during a 3-week period, with half of the animals in each group receiving dermal applications on abraded dorsal skin and the others receiving intradermal injections. After 2 weeks, the animals were challenged by application of terbacil to intact and abraded skin. The challenge application was repeated 2 weeks later.

Long-term Exposure

- Wazeter et al. (1964) administered terbacil, 82.7% (a.i.), in the diet to Charles River pathogen-free albino rats (20/sex/level) at levels of 0, 100, 500 or 5,000 ppm of a.i. for 90 days. This corresponds to doses of about 0, 5, 25 or 250 mg/kg/day based on the dietary assumptions of Lehman (1959). The parameters observed included body weight, food consumption, hematology, liver function tests, urinalyses, organ weights and gross and histologic pathology. No adverse effects with respect to behavior and appearance were noted. All rats survived to the end of the study. No effect on body weight gain was observed in either sex when terbacil was administered at 5 or 25 mg/kg/day. Females administered 250 mg/kg/day gained slightly less weight (15%) than controls. Males at this level showed no effect. No compound-related hematological or biochemical changes were found, and urinalyses were normal at all times. No gross or microscopic pathological changes were noted in animals administered terbacil at 5 or 25 mg/kg/day. Morphological changes in animals receiving the highest dose level were limited to the liver and consisted of statistically significant increases in liver weights. This change was accompanied by a moderate-to-marked hypertrophy of hepatic parenchymal cells associated with vacuolation of scattered hepatocytes. Similar microscopic changes, but with reduced severity, were found in one rat at the 25 mg/kg/day level. This study identified a Lowest-Observed-Adverse-Effect Level (LOAEL) of 25 mg/kg/day and a No-Observed-Adverse-Effect Level (NOAEL) of 5 mg/kg/day.

- Goldenthal et al. (1981) administered terbacil (97.8% a.i.) in the diet to CD-1 mice (80/sex/level) at levels of 0, 50, 1,250 or 5,000 to 7,500 ppm for 2 years. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day; therefore, these levels correspond to doses of about 0, 7.5, 187 or

750 to 1,125 mg/kg/day. The 5,000-ppm dose level was increased slowly to 7,500 ppm by week 54 of the study. Mortality was significantly higher ($p < 0.05$) in mice at the high dosage levels throughout the study. No changes considered biologically important or compound-related occurred in the hematological parameters. An increased incidence of hepatocellular hypertrophy was seen microscopically in male and female mice administered 750 to 1,125 mg/kg/day and in male mice administered 187 mg/kg/day. An increased incidence of hyperplastic liver nodules also occurred in male mice administered 750 to 1,125 mg/kg/day. Female mice from the 187-mg/kg/day group and both male and female mice from the 7.5-mg/kg/day group were free of compound-related microscopic lesions. This study identified a LOAEL of 187 mg/kg/day and a NOAEL of 7.5 mg/kg/day.

° Wazeter et al. (1967b) administered terbacil (80% a.i.) in the diet to Charles River CD albino rats (36/sex/level) at levels of 0, 50, 250 or 2,500 ppm to 10,000 ppm of a.i. for 2 years. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of a rat corresponds to 0.05 mg/kg/day; therefore, these dietary levels correspond to doses of about 0, 2.5, 12.5 or 125 to 500 mg/kg/day. The 2,500 ppm level was increased slowly to 10,000 ppm by week 46 of the study. No adverse compound-related alterations in behavior or appearance occurred in any test group. No significant differences in body weight gain in males and females administered 2.5 or 12.5 mg/kg/day were observed. Rats administered 125 to 500 mg/kg/day exhibited a significantly lower rate of body weight gain. This difference occurred early and became more pronounced with time in the female rats than in the male rats. Maximum differences were 14 to 17% in the male rats and 24 to 27% in the females when compared to the controls. No compound-related gross pathological lesions were seen at necropsy in rats from any groups. The only compound-related variation in organ weights was a slight increase in liver weights among rats from the 125- to 500-mg/kg/day dose level at final sacrifice. Histological changes were observed in the livers of rats fed terbacil at 12.5 mg/kg/day for 1 year and in the high-dose group fed 125 to 500 mg/kg/day for 1 and 2 years. These changes consisted of enlargement and occasional vacuolation of centrilobular hepatocytes. Due to an outbreak of respiratory congestion observed in all study groups at week 27, all animals were placed on antibiotic treatment (tetracycline hydrochloride), and the therapy was successful. This study identified a LOAEL of 125 to 500 mg/kg/day, based on irreversible histological changes in the liver, and a NOAEL of 12.5 mg/kg/day.

° Wazeter et al. (1966) administered terbacil (80% a.i.) in the diet to young purebred beagle dogs (4 to 6 months old, four/ sex/dose) at dose levels of 0, 50, 250 or 2,500 to 10,000 ppm of a.i. for 2 years. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of a dog corresponds to 0.025 mg/kg/day; therefore, these dietary levels correspond to approximately 0, 1.25, 6.25 or 62.5 to 250 mg/kg/day. The 2,500-ppm level was gradually increased to 10,000 ppm from week 26 to week 46 of the study. All animals underwent periodic physical examinations, hematologic tests, and determinations of 24-hour alkaline phosphatase, prothrombin time, serum glutamate oxaloacetate transaminase

(SGOT), serum glutamate pyrurate transaminase (SGPT) and cholesterol. No adverse compound-related alterations in behavior or appearance occurred among any of the control or treated dogs. No mortalities occurred during the 2-year course of treatment. Although there were some fluctuations in body weight throughout the study, these were not considered to be compound-related. No alterations in hematology, plasma biochemistry or urinalysis were observed. No compound-related gross or microscopic pathological changes were seen in any of the dogs sacrificed after 1 or 2 years of feeding. A slight increase in relative liver weights and elevated alkaline phosphatase occurred in dogs from the 62.5- to 250-mg/kg/day group and the 6.25-mg/kg/day group, which were sacrificed after 1 or 2 years. Also at 6.25 mg/kg/day, there was an increase in thyroid-to-body weight ratio. This study identified a LOAEL of 6.25 mg/kg (250 ppm) and a NOAEL of 1.25 mg/kg/day (50 ppm).

Reproductive Effects

- Wazeter et al. (1967a) administered terbacil (80% a.i.) in the diet to male and female Charles River CD rats of three generations (10 males and 10 females per level per generation) at dietary levels of 0, 50 or 250 ppm of a.i. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of a rat is equivalent to 0.05 mg/kg/day; therefore, these dietary levels correspond to doses of about 2.5 or 12.5 mg/kg/day. Each parental generation was administered terbacil in the diet for 100 days prior to mating. No abnormalities in behavior, appearance or food consumption of the parental rats were observed in any of the three generations. Males at the 12.5 mg/kg/day level in all three generations exhibited reduced body weight gains. Females in all three generations were similar to controls in body weight gain. No abnormalities were observed in the breeding cycle of any of the three generations relative to the fertility of the parental male and female rats, development of the embryos and fetuses, abortions, deliveries, live births, sizes of the litters, viability of the newborn, survival of the pups until weaning or growth of the pups during the nursing period. Gross examination of pups surviving at weaning from both litters of all three generations did not reveal any evidence of abnormalities. No compound-related histopathological lesions were observed in any of the tissues examined from weanlings of the F_{3b} litter. This study identified a LOAEL of 12.5 mg/kg/day and a NOAEL of 2.5 mg/kg/day.

Developmental Effects

- E.I. DuPont (1984a) administered terbacil by gavage as a 0.5% suspension in methyl cellulose to groups of 18 female New Zealand White rabbits (5 months old) from days 7 to 19 of gestation at dose levels of 0, 30, 200 or 600 mg/kg/day. Maternal mortality was significantly increased ($p \leq 0.05$) at the 600-mg/kg/day level. Additional indicators of maternal toxicity at 600-mg/kg/day were a significant increase ($p \leq 0.05$) in adverse clinical signs (anorexia and liquid or semi-solid yellow, orange or red discharges found below the cages) and a significant decrease ($p < 0.05$) in body weight gain. Mean body weight gains and the incidence of adverse effects were similar in controls and in the 30- and 200-mg/kg/day groups. Fetal toxicity at doses of 600 mg/kg/day included a significant decrease ($p \leq 0.05$) in fetal body weight and a significant increase ($p \leq 0.05$) in the frequency of extra ribs and partially ossified and unossified phalanges and pubes. This increase was not due to a statistically significant increase in any specific malformation, and occurred only at a dosage level that was overtly toxic to the dams, suggesting to the authors that it may be the result of maternal toxicity. No increase in the incidence of adverse effects was noted among fetuses produced by animals administered 30 or 200 mg/kg/day terbacil. Based on maternal and fetal toxicity, this study identified a LOAEL of 600 mg/kg/day and a NOAEL of 200 mg/kg/day.

° Culik et al. (1980) administered terbacil (96.6% a.i.) in the feed to female Charles River CD rats from days 6 to 15 of gestation at levels of 0, 250, 1,250 or 5,000 ppm. Based on the measured food consumption, these dietary levels correspond to doses of about 0, 23, 103 or 391 mg/kg/day. Maternal parameters observed included clinical signs of toxicity and changes in behavior, body weight and food consumption. Statistically significant ($p \leq 0.05$), compound-related reductions in mean body weight, weight gain and food consumption were seen in animals administered 103 or 391 mg/kg/day. No other clinical signs or gross pathological changes were observed in any animals. The mean number of live fetuses per litter and mean final maternal body weight were significantly lower ($p \leq 0.05$) in the groups administered 103 or 391 mg/kg/day than in the control group; the mean number of implantations per litter was also significantly lower ($p \leq 0.05$) than in control animals. Anomalies occurred in the renal pelvis, and ureter dilation was found in all the treatment groups. This study identified a LOAEL (lowest dose tested) of 23 mg/kg/day, based on anomalies of the renal pelvis and ureter dilation.

Mutagenicity

° E.I. DuPont (1984b) reported that terbacil did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes (0.01 and 1.0 uM), did not exhibit mutagenic activity in the CHO/HGPRT assay (0 to 5.0 uM) with or without metabolic activation, and did not produce statistically significant differences between mean chromosome numbers, mean mitotic indices or significant increases in the frequency of chromosomal aberrations when tested by in vivo bone marrow chromosome studies in Sprague-Dawley CD rats (15/sex/level) administered a single dose of terbacil by gavage at 0, 20, 100 or 500 mg/kg.

° Murnik (1976) reported that terbacil significantly elevated the rates of apparent dominant lethals when tested in *Drosophila melanogaster*, but the authors concluded that the significant reductions in egg hatch were probably due to physiological toxicity of the treatment, since genetic assays did not indicate the induction of chromosomal breakage or loss.

Carcinogenicity

- Goldenthal et al. (1981) administered terbacil (97.8% a.i.) in the diet to CD-1 mice (80/sex/level) at levels of 0, 50, 1,250 or 5,000 to 7,500 ppm for 2 years. These levels correspond to doses of about 0, 7.5, 187 or 750 to 1,125 mg/kg/day (Lehman, 1959). The 5,000-ppm dose level was increased slowly to 7,500 ppm by week 54 of the study. No increased incidence of cancer in the treated animals was found.
- Wazeter et al. (1967b) administered terbacil (80% a.i.) in the diet to Charles River CD albino rats (36/sex/level) at levels of 0, 50, 250 or 2,500 to 10,000 ppm of active ingredient for 2 years. These levels correspond to doses of about 0, 2.5, 12.5 or 125 to 500 mg/kg/day (Lehman, 1959). No evidence of compound-related carcinogenic effects was noted.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for terbacil. It is, therefore, recommended that the Ten-day HA value for a 10-kg child, 0.25 mg/L (300 ug/L), calculated below, be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The dietary reproductive study in rats by Wazeter et al. (1967a) has been selected to serve as the basis for the Ten-day HA value for terbacil. It identifies a LOAEL of 12.5 mg/L, based on a reduced body weight gain in the males in all three generations, and a NOAEL of 2.5 mg/kg/day. The teratology study in rats by Culik et al. (1980) provides support for this conclusion. This teratology study identifies a LOAEL of 23 mg/L (no doses lower than 23 mg/kg/day were tested) and essentially the same Ten-day HA value (0.23 mg/L) can be derived from this LOAEL by using an uncertainty factor of 1,000.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(2.5\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.25\ \text{mg/L}\ (300\ \text{ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of reduced body weight gain in male rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The dietary reproductive study in rats by Wazeter et al. (1967a) has been selected to serve as the basis for the Longer-term HA values for terbacil. A NOAEL of 2.5 mg/kg/day is identified in this study. A 90-day subchronic study in rats (Wazeter et al., 1964) identifying a NOAEL of 5 mg/kg/day supports this conclusion.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(2.5\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.25\ \text{mg/L}\ (300\ \text{ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of reduced body weight gain in male rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(2.5 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.875 \text{ mg/L } (900 \text{ ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of reduced body weight gain in male rats.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year dog feeding study by Wazeter et al. (1966), selected to serve as the basis for the Lifetime HA value for terbacil, identifies a NOAEL of 1.25 mg/kg/day, based on relative liver weight increases and an increase in alkaline phosphatase. A number of other studies provide information that supports the conclusion that the overall NOAEL for lifetime exposure of rats, mice and dogs to terbacil is less than 25 mg/kg/day. These include a 2-year feeding study in mice that identifies a NOAEL of 7.5 mg/kg/day for liver changes (Goldenthal, 1981) and a 2-year feeding study in rats that identifies a NOAEL of 12.5 mg/kg/day for lower body weight gain and liver effects (Wazeter et al., 1967b).

Using a NOAEL of 1.25 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(1.25 \text{ mg/kg/day})}{(100)} = 0.013 \text{ mg/kg/day (rounded from 0.0125 mg/kg/day)}$$

where:

1.25 mg/kg/day = NOAEL, based on slight increase in relative liver weight and elevated alkaline phosphatase.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.0125 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.44 \text{ mg/L } (400 \text{ ug/L})$$

where:

0.0125 mg/kg/day = RfD.

70 kg = assumed body weight of adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.44 \text{ mg/L})\ (20\%) = 0.09 \text{ mg/L } (90 \text{ ug/L})$$

where:

0.44 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of terbacil.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), terbacil may be classified in Group E: evidence of noncarcinogenicity for humans. This category is used for substances that show no evidence of carcinogenicity in at least two adequate animal tests or in both epidemiologic and animal studies. Studies by Goldenthal et al. (1981) and Wazeter et al. (1967b) reported no induction of any carcinogenic effect in mice or rats, respectively, administered terbacil in the diet for 2 years.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Tolerances have been established for residues of terbacil in or on many agricultural commodities by the U.S. EPA Office of Pesticide Programs (U.S. EPA, 1985a).

VII. ANALYTICAL METHODS

- Analysis of terbacil is by a gas chromatographic (GC) method applicable to the determination of certain organonitrogen pesticides in water samples (U.S. EPA, 1987). This method requires a solvent extraction of approximately 1 L of sample with methylene chloride using a separatory funnel. The methylene chloride extract is dried and exchanged to acetone during concentration to a volume of 10 mL or less. The compounds in the extract are separated by gas chromatography, and the measurement is made with a thermionic bead detector. This method has been validated in a single laboratory, and the estimated detection limit for terbacil is 4.5 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Treatment technologies currently available have not been tested for their effectiveness in removing terbacil from drinking water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

August, 1988

TERBUFOS

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

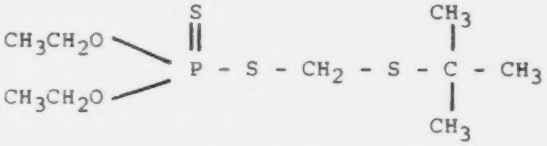
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 13071-79-9

Structural Formula



S-[[(1,1-Dimethylethyl)thio]methyl]O,O-diethyl phosphorodithioate

Synonyms

- Counter; Contraven (Meister, 1986).

Uses

- Control of corn rootworm and other soil insects and nematodes infesting corn. Control of sugarbeet maggots in sugarbeets; green bug on grain sorghum (Meister, 1986).

Properties (Windholz et al., 1983; Meister, 1986)

Chemical Formula	$C_9H_{21}O_2PS_3$
Molecular Weight	288.41
Physical State (room temp.)	Clear, slightly brown liquid
Boiling Point	69°C/0.01 mm Hg
Melting Point	-29.2°C
Density (24°C)	1.105
Vapor Pressure (25°C)	34.6 mPa
Specific Gravity	1.1
Water Solubility (25°C)	15 mg/L
Log Octanol/Water Partition Coefficient	595
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--
Technical	87 to 97% pure

Occurrence

- Terbufos has been found in 134 of 2,016 surface water samples analyzed and in 0 of 283 ground water samples (STORET, 1988). The 85th percentile of all nonzero samples was .10 ug/L in surface water with a maximum concentration found was 2.25 ug/L. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- ^{14}C Terbufos hydrolyzes rapidly in buffer solutions (Miller and Jenney, 1973). At a concentration of 4.6 ppm, the hydrolosis half-lives were 4.5, 5.5 and 8.5 days at pH 5, 7, and 9, respectively. Principal hydrolysis products were identified as formaldehyde (accounting for 50-70% of the applied radioactivity), t-butyl mercaptan, and O,O-diethylphosphorodithioic acid.

- ^{14}C Terbufos photodegrades rapidly on silica gel glass surfaces (Miller and Jenney, 1973). Approximately 30% of the radioactivity was recovered as terbufos within 8 days.

- Terbufos degrades with a half-life of about 10 days in a silt loam soil under aerobic conditions (USEPA, 1977). Terbufos residues dissipate fairly rapidly in the field. In Illinois, residues from application of terbufos (Counter 15-G) at 1 lb ai/A dissipated to 0.31 ppm within 40 days; residues were non-detectable (<0.05 ppm) by day 135 (Steller et al., 1973a). In Colorado, residues from a similar application of terbufos declined from 5.9 ppm to 1.56 ppm 100 days later; residues of 0.15 ppm were present at 309 days after application

- ^{14}C Terbufos residues are immobile in four different soil types: sand and sandy loam from New Jersey, Wisconsin silt loam and a North Dakota silt clay (Hui, 1973). Terbufos residues were slightly more mobile when sandy loam soil was aged for 30 days before leaching it with 22.5 inches of water - 18% of the applied radioactivity was detected in the 3.5 to 7.0 inch layer. Formaldehyde was the only degradate identified (Steller et al., 1973b)

III. PHARMACOKINETICS

Absorption

- North (1973) reported that 83% of a single oral dose of technical ^{14}C-terbufos (0.8 mg/kg) was excreted in the urine of rats 168 hours after dosing. (The carbon atom of the thiomethyl portion of terbufos was radiolabeled.) An additional 3.5% was recovered in feces. This study indicates that terbufos was well absorbed (about 80 to 85%) from the gastrointestinal tract.

Distribution

- North (1973) reported that maximum residues of cholinesterase-inhibiting compounds (phosphorylated metabolites), resulting from a single oral dose of technical ^{14}C-terbufos (0.8 mg/kg) given to rats, were found in rat liver (0.08 ppm) 6 hours after dosing. In the same study, residues of hydrolysis (nonphosphorylated metabolites) products reached a maximum in rat kidney 12 hours after dosing (0.9 ppm). After 168 hours, each body tissue in the rat contained less than 0.1 ppm radiolabeled) terbufos.

Metabolism

- North (1973) reported that terbufos was extensively metabolized in the rat. ^{14}C-Radiolabeled terbufos was administered in a single dose to 16 male Wistar rats at a dose level of 0.8 mg/kg via gavage. Examination of urine extracts by thin-layer chromatography (TLC) showed the presence of 10 radiometabolites in the rat urine. Approximately 96% of the radioactivity present in the urine was composed of an S-methylated series of metabolites, which result from the cleavage of the sulfur-phosphorus bond, methylation of the liberated thiol group and oxidation of the resulting sulfide to sulfoxides and sulfones. Of the remaining radioactivity, about 2% was composed of various oxidation products of the intact parent organophosphorus compound and 2% was an unknown metabolite.

Excretion

- North (1973) reported that technical terbufos and its metabolites were rapidly excreted in the urine of the rat. Radiolabeled terbufos was administered in a single dose to male Wistar rats at a dose level of 0.8 mg/kg by gavage. Of all the radioactivity recovered in the urine, 50% was excreted after 15 hours. After 168 hours, the termination of the test, 83% of the terbufos was excreted via the urine and 3.5% was recovered in the feces.

IV. HEALTH EFFECTS

Humans

- Peterson et al. (1984) reported the results of farm worker exposure to Counter 15-G (a 15% granular formulation of terbufos). Five farmers (one loader, one flagger and three scouts) were exposed for varying time periods (loader, 5 minutes; flagger, 15 minutes; scouts, twice for 30 minutes) during a typical workday while Counter 15-G was applied aerially to a young corn crop. The mean exposure via inhalation was <0.25 ug/hour, the sensitivity of the monitoring method, for all samples collected. The exposure values for the five farm workers were: 331 ug/hour for the loader, 0 ug/hour for the flagger, 381 ug/hour for scouts (after 3 days) and 250 ug/hour for scouts (after 7 days). All of the farm workers were men and weighed between 65.9 and 90.9 kg. Analysis of urinary metabolites showed no indication of significant absorption by any of the exposed workers. For example, all urinary alkyl phosphate analyses were negative (detection level, 0.1 ppm). Plasma and red blood cell cholinesterase values of the exposed workers showed no significant (95% confidence level) decrease in activity when compared to pre-exposed samples, indicating no adverse physiological effects from exposures.

- Devine et al. (1985) reported results similar to Peterson et al. (1984) for 11 farmers who were exposed to terbufos during a typical workday while planting corn and applying Counter 15-G. The average estimated dermal exposure was 72 ug/hour, and the estimated respiratory exposure was 11 ug/hour. The results of urinary alkyl phosphate analyses were all negative, showing no detectable absorption of terbufos. Plasma and red blood cell cholinesterase (ChE) values of the exposed farmers showed no significant difference in activity when compared to pre-exposure or control values, indicating no adverse physiological effects from the exposure. The report concluded that, based on the study results, the use of Counter 15-G does not present a significant hazard, in terms of acute toxicity, to farmers using this product for the control of corn insects.

Animals

Short-term Exposure

- Parke and Terrell (1976) reported that the acute oral LD_{50} value of technical-grade (86%) terbufos in Wistar rats was 1.73 mg/kg. Terbufos was administered in doses of 1.0 to 3.0 mg/kg via gavage in corn oil to a total of 50 rats (25 female/25 male; 10/dose). Average weight of the rats ranged from 200 to 300 g. The lowest dose (1.0 mg/kg) did not result in any mortality. Observed effects to the rats were: respiratory depression, piloerection, clonic convulsions, exophthalmus, ptosis, lacrimation, hemorrhage and decreased motor activity.

- Consultox Laboratories (1975) reported that the acute oral LD_{50} value of technical-grade (86%) terbufos in male Wistar rats was 1.5 mg/kg. Terbufos was administered by gavage in doses of 0.50 to 2.5 mg/kg to a total of 50 male rats (10/dose) at an average weight of 200 ± 20 g. No mortality was reported at the low dose (0.50 mg/kg). Ten percent mortality was reported at the 0.75-mg/kg dose. Other effects reported were: salivation, diuresis, diarrhea, disorientation, chromodocryorrhea, piloerection and body tremors.

- American Cyanamid (1972a) reported acute oral LD_{50} values (for 96.7% technical-grade terbufos) in dogs, mice and rats of 4.5 mg/kg (male)/ 6.3 mg/kg (female), 3.5 mg/kg (male)/9.2 mg/kg (female), and 4.5 mg/kg (male)/ [illegible].0 mg/kg (female), respectively. No details were given as to age or weight.

- American Cyanamid (1972b) reported additional acute oral LD_{50} values in male Wistar rats and female CF1 mice of 1.6 mg/kg and 5.0 mg/kg, respectively. Other effects reported included cholinesterase inhibition in both sexes.

- Berger (1977) reported that plasma ChE was inhibited by as much as 79% in eight beagle dogs that were dosed via corn oil with 0.05 mg/kg/day (only dose tested) technical terbufos for 28 days. Red blood cell ChE was not inhibited at the dose tested.

- **Tegeris Labs** (1987) fed dogs (6/sex/dose) technical terbufos **(purity 89.6%)** in a corn oil vehicle (capsule) at doses of 0, 1.25, 2.5, 5.0, and 15 ug/kg/day for 28 days in order to define a plasma cholinesterase NOAEL which was not previously defined in a one year study conducted by American Cyanamid (1986). Based upon the evaluation of plasma, RBC and brain chloinesterase (ChE) activities at 1, 2, and 4 weeks during a 28 day dosing regime, a plasma ChE activity LOAEL (ranging from 10-20% depression) was determined to be 2.5 ug/kg/day in male and female dogs. A plasma ChE NOAEL was identified at 1.25 ug/kg/day.

Dermal/Ocular Effects

- Kruger et al. (1973) conducted a subacute dermal toxicity test in New Zealand White rabbits. Technical-grade terbufos was administered at doses varying from 0.004 to 0.1 mg/kg to the shaved, intact or abraded backs of male and female rabbits (2.5 to 3.5 kg). All animals survived the 30-day test and showed no adverse effects with regard to food and water intake, elimination, behavior, pharmacological effects and weight gain differences. There were no observed changes in hematological determinations (hematocrit, total erythrocyte and total leukocyte levels). Minor changes reported were increased numbers of eosinophils and basophils in all groups, occasional minimal edema that abated by day 21, and occasional mild erythema. All observed changes occurred on intact and abraded skin sites.

- American Cyanamid (1972a,b) conducted a series of tests with 96.7 and 85.8% terbufos using New Zealand White rabbits. Twenty male rabbits (2.56 to 2.73 kg) were administered doses of 0.4 to 3.5 mg/kg terbufos to their shaved backs. Dermal contact with terbufos was maintained for 24 hours. The dermal LD_{50} value was 1.0 mg/kg. An acute dermal test with 96.7% terbufos resulted in an LD_{50} of 1.1 mg/kg in male rabbits (no other details were given). In another test with 96.7% terbufos, 0.5 mL (500 mg) of terbufos was applied to the backs of rabbits; all of these animals died within 24 hours after dosing.

- American Cyanamid (1972a) reported the results of an application of 0.1 mg of technical-grade (96.7%) terbufos to the eyes of New Zealand albino rabbits. All animals died within 2 to 24 hours after dosing.

Long-term Exposure

- **Daly et al.** (1979) administered terbufos (90% active ingredient [a.i.]) in the diet to groups of male and female Sprague-Dawley rats (20/sex/group, 24 to 39 days old, 95 to 150 g) at levels of 0, 0.125, 0.25, 0.5 or 1.0 ppm (estimated doses of 0, 0.01, 0.02, 0.046 or 0.09 mg/kg/day based on feed conversions given by the authors) for 90 days. Body weights and food consumption were measured weekly. Blood samples were obtained weekly and analyzed for plasma, and erythrocyte ChE. Brain ChE was analyzed at the study's termination. Body organs were weighed and analyzed for histopathology. The No-Observed-Adverse-Effect Level (NOAEL) was determined to be 0.02 mg/kg/day, based on the absence of effects on ChE. The statistically significant Lowest-Observed-Adverse-Effect Level (LOAEL) was determined to be 0.046 mg/kg based on the observed 17% decrease in plasma ChE in females. There were no depressions of erythrocyte or brain ChE at the highest dose tested (0.09 mg/kg/day). In addition, gross postmortem observations revealed no findings related to the test substance. Systemically, the LOAEL for increased liver weight in females and for a dose-related increase in liver extra-medullary hematopoiesis was 0.046 mg/kg/day. No other histological lesions were found to be compound-related. The systemic NOAEL based on absence of liver effects was determined to be 0.02 mg/kg in this study.

- Biodynamics Inc. (1987) administered terbufos (purity 89.6%) to Charles River CD rats (30/sex/dose) in a corn oil vehicle at doses of 0, 0.125, 0.5 and 1.0 ppm (estimated doses of 0.006, 0.025, and 0.05 mg/kg/day, based on Lehman (1959)) for one year. The systemic NOAEL was identified at 0.05 mg/kg/day, the highest dose tested. The cholinesterase NOAEL was defined at 0.025 mg/kg/day and the ChE LOAEL was observed at 0.05 mg/kg/day based on plasma and brain cholinesterase decreases (10-30%).

- Morgareidge et al. (1973) administered technical-grade terbufos in the diet to groups of male and female beagle dogs (four/sex/group, 10 to 13 months old, 9.0 to 13.8 kg) at levels of 0.0025, 0.01 and 0.04 mg/kg/day, 6 days a week for 26 weeks. Plasma, red blood cell and brain ChE levels, body weight and food, urinalysis, gross necropsy examination and histopathology were evaluated. Observed effects included a decrease in ChE activity in plasma at all dose levels; however, decreased ChE activity was statistically significant only for doses of 0.01 mg/kg/day and above. At 0.01 mg/kg/day, plasma ChE was inhibited by 26% and red blood cell ChE was inhibited by 14%. No statistical analyses were performed on body weight changes, food consumption, hematology, clinical chemistry, urinalyses and organ weight data. The LOAEL (based on ChE effects) determined in the study was 0.01 mg/kg/day and the NOAEL was determined to be 0.0025 mg/kg/day.

- Rapp et al. (1974) administered technical-grade terbufos in the diet to groups of Long-Evans rats (sixty/sex/dose, weanlings, 122 to 138.8 g) at levels of 0.25, 1.0, 2.0, 4.0, and 8.0 ppm for 2 years. These doses correspond to 0.0125, 0.05, 0.1, 0.2 and 0.4 mg/kg/day (Lehman, 1959. The original high doses (2.0 ppm) were increased to 4.0 and then to 8.0 ppm for males, and were increased from 2.0 to 4.0 to 8.0 and then reduced to 4.0 ppm for females. Body weight and food consumption were measured weekly. Hematology, clinical chemistry and urinalyses were also performed. Red blood cell ChE and brain ChE were significantly inhibited at 0.05 mg/kg/day (20% inhibition for brain ChE and 43% for red blood cell ChE in females) and above. Red blood cell ChE was also inhibited at 0.0125 mg/kg/day (12% in males and 15% in females). At the high dose (0.1 to 0.4 mg/kg/day), there was a noticeable decrease in mean body weight and mean food consumption. Mortality rates were 24 and 27% (males and females, respectively) at the high dose, 19%

(males) at the mid-dose and 10% (males) at the low dose. The incidence of exophthalmia was in high-dose females (exophthalmia was also noted in low- and mid-dose control females). This study did not establish a NOAEL. The LOAEL was equivalent to the lowest dose tested (0.0125 mg/kg/day).

- McConnell (1983) conducted a follow-up pathology study of the results obtained from Rapp et al. 1974. Effects reported were gastric ulceration and/or erosion of glandular and nonglandular stomach mucosa in high-dose rats. No similar effect was seen in low and mid-dose rats. Acute bronchopneumonia and granuloma of lungs occurred in high-dose rats more frequently than in low-dose, mid-dose or control rats. The authors reported that lung inflammation did not appear directly associated with the compound.

- Shellenberger (1986) administered technical-grade terbufos (89.6% a.i.) in capsule form to groups of beagle dogs (six/sex/dose, 6.8 to 7.5 kg, 5 to 6 months old) at doses of 0, 0.015, 0.120, 0.240 and 0.480 mg/kg/day for 1 year. The high doses were eventually reduced to 0.090 and 0.060 mg/kg/day after the 8th week of the study. Body weight and food consumption were measured together with assessment of urinalyses, organ weights and cholinesterase levels. One male and one female at the high dose and one female at 0.240 mg/kg/day were found dead. At the two highest doses (0.240 and 0.480 mg/kg/day), decreased body weights and food consumption were observed. Mean erythrocytic parameters of high-dose males and females were significantly reduced at 3 months but not at 6 months or at termination of the study. Plasma ChE activity was significantly inhibited to 55% of controls at 0.015 mg/kg/day. Slight inhibition of erythrocyte ChE activity occurred at 0.120 mg/kg/day in females but not in males. No inhibition of erythrocyte ChE in males or females was observed at the lower doses. Brain ChE activities were similar for both sexes at all dose levels. Urinalyses and organ weight data revealed no significant differences. The report suggests that the NOAEL was 0.120 mg/kg/day in males and 0.090 mg/kg/day in females based on lack of erthrocyte ChE inhibition.

- American Cyanamid (1986) administered terbufos (purity 89.6%) in corn oil vehicle (capsule) to beagle dogs (6/sex/dose) at doses of 0, 0.015, 0.06, 0.09 and 0.12 mg/kg/day for one year. The major effect of terbufos was upon cholinesterase activity. There was a substantial depression in male and female dog plasma cholinesterase activity (30-60%) in all treatment groups compared against controls at week 13 through 52. RBC ChE activity in all dogs was moderately inhibited (20%) in both mid and high doses. Brain ChE inhibition was more variable but depression in ChE activity was apparent at mid and high doses. There was no evidence of compound-related effect upon mean organ weights or organ-body or brain we[illegible] ratios nor upon histopathology of non-neoplastic lesions. [illegible] plasma ChE NOAEL could not be established. The LOAEL for this study was identified as 0.015 mg/kg/day, the lowest dose tested.

Reproductive Effects

- Smith and Kasner, (1972a) administered technical terbufos via the diet to Long-Evans and Blue Spruce rats (10 males/dose, weighing 276.3 g; 20 females/dose, weighing 185.6 g) for a period of 6 months at levels of 0, 0.25 and 1 ppm. These levels correspond to doses of 0, 0.0125 and 0.05 mg/kg/day, based on a conversion factor of 0.05 for rats (Lehman, 1959). The first parental generation (F_0) was dosed for 60 days. A reproductive LOAEL of 0.05 mg/kg was determined based on an increased percentage of litters with dead offspring in each of 3 generations as compared to controls. A NOAEL of 0.0125 mg/kg was identified.

Developmental Effects

- MacKenzie (1984) administered terbufos (87.8% a.i.) by gavage to groups of 18 female New Zealand White rabbits (3.5 kg) at levels of 0, 0.1, 0.2 and 0.4 mg/kg/day on days 7 to 19 of gestation. Reproductive indices monitored were female mortality, corpora lutea or implants, sex ratio, implantation efficiency, fetal body weight, fetal mortality and skeletal development. Cesarean sections were performed on day 29 of gestation. Survival of adult female rabbits was 100% in controls and in the 0.2-mg/kg/day dose group; 89% in the 0.1-mg/kg/day dose group; and 67% in the high-dose (0.4 mg/kg/day) group. There were no statistically significant dose-related differences in mean body weight, weight changes or gravid uterine weights, mean number of corpora lutea, implantation efficiency, sex ratio, fetal body weight or number of live or resorbing fetuses. The incidence of fetuses with accessory left subclavian artery was significantly greater in the high-dose (0.4 mg/kg/day) group. The incidence of an extra unilateral rib and of chain fusion of sternebrae was significantly lower in the high-dose group than in the controls. According to the author, terbufos appears to be maternally toxic at 0.4 mg/kg/day, the highest dose tested.

- Rodwell (1985) administered terbufos (87.8% a i.) via gavage to groups of 25 Charles River female rats (226 to 282 g, 71-days old) at doses of 0.05, 0.10 and 0.20 mg/kg/day on days 6 to 15 of gestation. Cesareans sections were performed on day 20; half of the fetuses were stained for skeletal evaluation. Parent survivability, body weight and embryonic and fetal development were all assessed. All parents survived the test. No changes in general appearance or behavior were observed. No doses led to teratogenic effects. Slightly decreased maternal mean body weights were observed during days 12 to 16 and following treatment in the 0.10- and 0.20-mg/kg/day dose groups. The study demonstrates that terbufos is slightly maternally toxic at dose levels of 0.10 and 0.20 mg/kg/day. A maternal NOAEL of 0.05 mg/kg/day, the lowest dose tested, was identified.

Mutagenicity

- Thilager et al. (1983) reported that Chinese hamster ovary cells tested with and without S-9 rat liver activation at concentrations of 100, 50, 25, 10, 5 and 2.5 nL/mL (ppm) terbufos (purity not specified) did not cause any significant increase in the frequencies of chromosomal aberrations. Only a concentration of 100 nL/mL proved to be cytotoxic.

- Allen et al. (1983) conducted mutagenicity tests with terbufos (87.8% a.i.) in the presence of S-9 metabolic activation and Chinese hamster ovary cells and in the absence of S-9 activation. Initial tests were conducted with doses of 100 to 10 ug/L, and then followed up with S-9 activation at doses of 50, 42, 33, 25, 10 and 5 ug/ml. Terbufos proved to be cytotoxic at 75 to 100 ug/mL with activation and at 50 to 70 mg/mL without activation. There were no increases in the frequency of chromosomal aberrations. The authors concluded that terbufos reflected a negative mutagenic potential.

- Godek et al. (1983) conducted a rat hepatocyte primary culture/DNA repair test with terbufos (87.8% a.i.) at doses ranging from 100 to 33 ug/well (a well contains 2 mL of media). Unscheduled DNA repair synthesis was quantified by a net nuclear increase of black silver grains for 50 cells/slide. This value was determined by taking a nuclear count and three adjacent cytoplasmic counts (100 ug/well was cytotoxic). The results for terbufos were negative in the rat hepatocyte primary culture/DNA repair test. These findings are based on the inability of terbufos to produce a mean grain count of 5 or greater than the vehicle-control mean grain count at any level. The authors concluded that terbufos reflected a negative mutagenic potential.

Carcinogenicity

- Rapp et al. (1974a) administered technical terbufos in the diet to groups of mice (75/sex/dose) at levels of 0, 0.5, 2.0 and 8.0 ppm for 18 months. These doses correspond to 0.075, 0.3 and 1.2 mg/kg/day (Lehman, 1959). The authors reported no signs of tumors or neoplasia. Effects noted include alopecia and signs of ataxia; exophthalmia in males, corneal cloudiness and opacity and eye rupture. Organ tissues examined were liver, kidney, heart and lung. No pathological changes attributable to terbufos were observed in these four organs.

- Rapp et al. (1974b) administered technical terbufos in the diet to groups of Long-Evans rats (60/sex/dose) at levels of 0, 0.25, 1.0, 2.0, 4.0 and 8.0 ppm for 2 years. These doses correspond to 0.0125, 0.05, 0.1, 0.2 and 0.4 mg/kg/day (Lehman, 1959). There were no indications of tumorigenic effects at any dose tested.

- McConnell (1983) conducted a follow-up pathology evaluation of the results obtained from Rapp et al (1974b) and concluded that the compound had no effect on tumorigenesis.

- **Tegeris Labs, Inc.** (1986) administered terbufos (purity 89.6%) in the diet to groups of Charles River CD-1 mice (65/sex/dose) at levels of 0, 3, 6, and 12 ppm for 18 months. These doses correspond to 0.45, 0.90, and 1.8 mg/kg/day based on Lehman (1959). At these dose levels there was no indication of oncogenic effect.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for the determination of the One-day HA value for terbufos. It is, therefore, recommended that the Ten-day HA value for a 10-kg child (0.005 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The teratogenicity study in rats by Rodwell (1985) has been selected to serve as the basis for the Ten-day HA value for terbufos. Pregnant rats administered terbufos via gavage at a level of 0.05 mg/kg/day from day 6-15 of gestation showed no clinical signs of toxicity in the adult animals and no reproductive or teratogenic effects in the fetuses. The study identified a NOAEL of 0.05 mg/kg/day. These results are supported by the results of studies by MacKenzie (1984) with rabbits and by Smith and Kasner (1972a) with rats. In addition, the Rodwell (1985) study is of a most appropriate duration (10 days) for deriving a 10-day HA.

Using a NOAEL of 0.05 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.05\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 0.005\ \text{mg/L}\ (5\ \text{ug/L})$$

where:

0.05 mg/kg/day = NOAEL, based on the absence of clinical signs of toxicity and the lack of reproductive or teratogenic effects in rats exposed to terbufos via gavage for 10 days during gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisories

The 28-day feeding study in beagle dogs by Tegeris Labs (1987) has been selected to serve as the basis for the Longer-term HA value for terbufos. In this study, dogs were administered terbufos in a corn oil vehicle (capsule) at doses of 1.25, 2.5, 5.0 and 15 ug/kg/day. A plasma cholinsterase NOAEL, which was not previously defined in a one year dog study conducted by American Cyanamid (1986), was defined at 1.25 ug/kg/day in the Tegeris Lab (1987) study. The plasma ChE LOAEL was determined to be 2.5 ug/kg/day based on decreased plasma ChE activity in male and female dogs. Other studies of longer duration were not selected for a number of reasons. First, the Tegeris Labs (1987) study was designed to define the plasma ChE NOAEL which was not achieved in the one year study conducted by American Cyanamid (1986). It is a follow-up study employing the same parameters as the American Cyanamid (1986) study, only the doses are lower. The results of the two studies, evaluated together, adequately define the chronic endpoint of ChE activity depression. In other studies, the ChE NOAEL is either an order of magnitude larger than the NOAEL defined by Tegeris Labs (1987) or only a LOAEL has been defined. For example, Daly et al. (1979) identified a NOAEL an order of magnitude higher as is also the case in Shellenberger (1986). Rapp et al. (1974b) and American Cyanamid (1986) were rejected since these studies identified LOAELs only. Morgareidge et al. (1973) was rejected because there was a high degree of uncertainty associated with the actual dose consumed by the test animals.

Using a NOAEL of 0.0013 mg/kg/day, the Longer-term HA is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.0013\ \text{mg/kg/day})\ (10\ \text{kg})}{(10)\ (1\ \text{L/day})} = 0.0013\ \text{mg/L}\ (1.0\ \text{ug/L})$$

where:

0.0013 mg/kg/day = NOAEL, based on absence of inhibition of plasma cholinesterase in dogs exposed to terbufos 28 days.

10 kg = assumed body weight of a child.

10 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study. An uncertainty factor of 10 is chosen since the endpoint in question is cholinesterase inhibition which was not accompanied by any adverse systemic effects.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.0013\ \text{mg/kg/day})\ (70\ \text{kg})}{(10)\ (2\ \text{L/day})} = 0.0045\ \text{mg/L/day}\ (5\ \text{ug/L})$$

where:

0.0013 mg/kg/day = NOAEL, based on absence of cholinesterase inhibition in dogs exposed to terbufos for 28 days.

70 kg = assumed body weight of an adult.

10 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study. An uncertainty factor of 10 is chosen since the endpoint in question is cholinesterase inhibition which was not accompanied by any adverse systemic effects.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be derived (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 28-day feeding study in beagle dogs by Tegeris Labs (1987) has been selected to serve as the basis for the Longer-term HA value for terbufos. In this study dogs were administered terbufos in a corn oil vehicle (capsule) at doses of 1.25, 2.5, 5.0 and 15 ug/kg/day. A plasma cholinsterase NOAEL, which was not previously defined in a one year dog study conducted by American Cyanamid (1986), was defined at 1.25 ug/kg/day in the Tegeris Lab (1987) study. The plasma ChE LOAEL was determined to be 2.5 ug/kg/day based on decreased plasma ChE activity in male and female dogs. Other studies of longer duration were not selected for a number of reasons. First, the Tegeris Labs (1987) study was designed to define the plasma ChE NOAEL which was not achieved in the one year study conducted by American Cyanamid (1986). It is a follow-up study employing the same parameters as the American Cyanamid (1986) study, only the doses are lower. The results of the two studies, evaluated together, adequately define the chronic endpoint of ChE activity depression. In other studies, the ChE NOAEL is either an order of magnitude larger than the NOAEL defined by Tegeris Labs (1987) or only a LOAEL has been defined. For example, Daly et al. (1979) identified a NOAEL an order of magnitude higher as is also the case in Shellenberger (1986). Rapp et al. (1974b) and American Cyanamid (1986) were rejected since these studies identified LOAELs only. Morgareidge et al. (1973) was rejected because there was a high degree of uncertainty associated with the actual dose consumed by the test animals.

Using this study, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.0013 \text{ mg/kg/day})}{(10)} = 0.00013 \text{ mg/kg/day}$$

where:

0.0013 mg/kg/day = NOAEL, based on absence of inhibition of cholinesterase in dogs exposed to terbufos for 28 days.

10 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study. An uncertainty factor of 10 was chosen since the endpoint in question is cholinesterase inhibition which was not accompanied by any adverse systemic effects.

Step 2: **Determination of the Drinking Water Equivalent Level (DWEL)**

$$\text{DWEL} = \frac{(0.00013\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.0045\ \text{mg/L/day}\ (5.0\ \text{ug/L})$$

where:

0.00013 mg/kg/day = RfD

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.0045 mg/L) (20%) = 0.0009 mg/L (0.9 ug/L)

where:

0.0045 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of terbufos.
- The U. S. EPA's Cancer Assessment Group (CAG) has assessed the carcinogenic potential of terbufos and has concluded that there are not enough data to determine whether terbufos is carcinogenic.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), terbufos may be classified in Group D: not classified. This category is for substances with inadequate human and animal evidence of carcinogenicity. Although two carcinogenicity studies are available for at least two animals. these studies have been considered flawed by the Agency.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- No other criteria, guidance or standards were found in the available literature.

VII. ANALYTICAL METHODS

- Analysis of terbufos is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary collumn GC. Measurement is made using a nitrogen-phosphorus detector. This method has been validated in a single laboratory and estimated detection limits for analytes such as terbufos are estimated at 0.5 ug/l.

VIII. TREATMENT TECHNOLOGIES

- No data were found for the removal of terbufos from drinking water by conventional treatment.

- No data were found on the removal of terbufos from drinking water by activated carbon adsorption. However, due to its low solubility and high molecular weight, terbufos probably would be amenable to activated carbon adsorption.

- No data were found on the removal of terbufos from drinking water by ion exchange. However, the structure of this ester indicates that it is not ionic and thus probably would not be amenable to ion exchange.

- No data were found for the removal of terbufos from drinking water by aeration. However, the Henry's Coefficient can be estimated from available data on solubility (10 to 15 mg/L) and vapor pressure (0.01 mm Hg at 69°C). Terbufos probably would not be amenable to aeration or air stripping because its Henry's Coefficient is approximately 12 atm.

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*Confidential Business Information.

August, 1988

TRIFLURALIN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

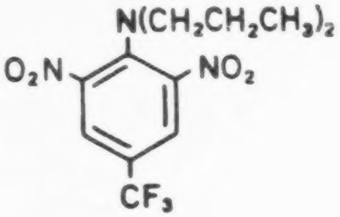
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1582-09-8

Structural Formula



alpha, alpha, alpha-Trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine

Synonyms

- 2,6-Dinitro-N, N-dipropyl-4-trifluoromethylaniline; Agreflan; Crisalin; Treflan; L-36352; Trifluralin (U.S. EPA, 1985a,b).

Uses

- A selective herbicide (preemergent) for control of annual grasses and broad-leafed weeds. Applied to soybean, cotton and vegetable crops; fruit and nut trees, shrubs; and roses and other flowers. Also used on golf courses, rights-of-way, and domestic outdoor and industrial sites (U.S. EPA, 1985b).

Properties

Chemical Formula	$C_{13}H_{16}F_3N_3O_4$
Molecular Weight	335.2
Physical State (25°C)	Orange, crystalline solid
Boiling Point	139 to 140°C
Melting Point	46 to 49°C
Density	--
Vapor Pressure (25°C)	1.1×10^{-4} mm Hg
Specific Gravity	--
Water Solubility (25°C)	0.3 mg/L
Log Octanol/Water Partition Coefficient	4.69
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Trifluralin does not have a strong potential ground water contaminant due to its strong adsorption to soil and negligible leaching (U.S. EPA, 1985b).

- Trifluralin has been detected in finished drinking water supplies (NAS, 1977).

- Trifluralin has been found in 172 of 2,047 surface water samples analyzed and in 1 of 507 ground water samples (STORET, 1988). Samples were collected at 249 surface water locations and 336 ground water locations, and trifluralin was found in 7 states. The 85th percentile of all nonzero samples was 0.54 ug/L in surface water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Trifluralin at 5 ppm degraded with 15% of the applied trifluralin lost after 20 days in a silt loam soil (aerobic metabolism) study (Parr and Smith, 1973). The samples were incubated in the dark at 25°C and 0.33 bar moisture.

- Trifluralin, applied alone or in combination with chlorpropham or chlorpropham plus PPG-124, dissipated with a half-life of 42 to 84 days in sandy loam or silt loam soil incubated at 72 to 75°F and 18% moisture content under laboratory conditions (Maliani, 1976).

- In an anaerobic soil metabolism study, trifluralin at 5 ppm degraded in nonsterile silt loam soil, with less than 1% of applied trifluralin detected after 20 days of incubation (0.33 bar moisture in the dark at 25°C; anaerobicity was maintained with nitrogen gas). Autoclaving and flooding the soil decreased the degradation rate of the compound (Parr and Smith, 1973).

- ^{14}C-Trifluralin at 1.1 kg/ha was relatively immobile in sand, sandy loam, silt, loam and clay loam soil columns (30-cm height) eluted with 60 cm of water, with more than 90% of the applied radioactivity remaining in the top 0- to 10-cm segment (Gray et al., 1982).

- Trifluralin concentrations in runoff (water/sediment suspensions) were less than 0.04% of the applied amount for 3 consecutive years following treatment at 1.4 kg/ha and 13 to 27 cm of rainfall (Willis et al., 1975). The field plots (silty clay loam soil, 0.2% slope) were planted with cotton or soybeans.

- In the field, ^{14}C-trifluralin (99% pure) at 0.84 to 6.72 kg/ha dissipated in the top 0- to 0.5 cm layer of a silt loam soil, with 14, 4, and 1.5% of the applied amount remaining 1, 2 and 3 years, respectively, after application (Golab et al., 1978). Approximately 30 minor degradates were identified and quantified; none represented more than 2.8% of the applied amount. Trifluralin (4 lb/gal EC) at 0.75 and 1.5 lb/A dissipated in a medium loam soil, with 20 and 32%, respectively, of the applied remaining 120 days after treatment (Helmer et al., 1969; Johnson, 1977).

- Trifluralin (4 lb/gal EC) dissipated from a sandy loam soil treated at 1.0 lb ai/A, with a half-life of 2 to 4 months (Miller, 1973).
- Trifluralin was detected in 107 soil samples taken nationwide at less than 0.01 to 0.98 ppm in fields treated with trifluralin at various rates for 1, 2, 3 or 4 consecutive years (Parka and Tepe, 1969).
- Trifluralin was detected in 12% of the soil samples taken from 80 sites in 15 states in areas considered to be regular pesticide-use areas based on available pesticide-use records (Stevens et al., 1970). Concentrations detected in soils ranged from less than 0.01 to 0.48 ppm. Trifluralin residues were detected in only 3.5% of the 1,729 agricultural soils sampled in 1969 (Wiersma et al., 1972).
- Trifluralin was detected at a maximum concentration of 0.25 ppm. Residues of volatile nitrosamines (dimethylnitrosoamine, N-nitro-sodipropylamine, or N-butyl-N-ethyl-N-nitrosoamine) were not detected in water samples taken from ponds and wells located in or near fields that had been treated with trifluralin at various rates (Day et al., 1977).

III. PHARMACOKINETICS

Absorption

- Emmerson and Anderson (1966) indicated that trifluralin is not readily absorbed from the gastrointestinal (GI) tract and that the fraction that is absorbed is completely metabolized. Of an orally administered dose (100 mg/kg), only 11 to 14% was excreted in the bile after 24 hours, indicating low enterohepatic circulation.

Distribution

- No information was found in the available literature on the distribution of trifluralin.

Metabolism

- Four metabolites of trifluralin were identified in rats. Twelve rats were given 100 mg/kg $^{14}CF_3$-trifluralin in corn oil by gavage for 2 weeks. The metabolites, identified by thin-layer chromatography, were produced by removal of both propyl groups or dealkylation and reduction of a nitro group to an amine (Emmerson and Anderson, 1966).
- An *in vitro* study using rat hepatic microsomes indicated that trifluralin undergoes aliphatic hydroxylation of the N-alkyl substituents, N-dealkylation and reduction of a nitro group (Nelson et al., 1976).
- There are insufficient data to characterize the general metabolism of trifluralin in animals (U.S. EPA, 1986a).

Excretion

- Rats given an oral dose (100 mg/kg) of $^{14}CF_3$-trifluralin excreted virtually all of the dose within 3 days. The radioactivity was excreted during the first 24 hours. Approximately 78% of the dose was eliminated in the feces and 22% in the urine (Emmerson and Anderson, 1966).

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- The Pesticide Incident Monitoring System database indicated 105 incident reports involving trifluralin from 1966 to April of 1981. Of the 105 reports, 49 cases involved humans exposed to trifluralin alone. Twenty-seven cases involved human exposure to mixtures containing trifluralin. The remaining incidents involved nonhuman exposures (U.S. EPA, 1981a).

- Among reports of human exposure to trifluralin alone, one fatality was reported. A 9-year-old girl suffered cardiac arrest following the ingestion of an unknown amount of trifluralin (U.S. EPA, 1981a).

- Verhalst (1974, as cited in U.S. EPA, 1985a) reported that the symptoms observed in trifluralin poisonings appeared to be related to the solvent used (e.g., acetone or xylene) rather than trifluralin itself.

Long-term Exposure

- The majority of reported trifluralin exposure cases were occupational in nature. Trifluralin exposure has resulted in dermal and ocular irritation in humans. Other reported symptoms include respiratory involvement, abdominal cramps, nausea, diarrhea, headache, lethargy and parasthesia following dermal or inhalation exposure. Specific exposure levels or durations were not reported (U.S. EPA, 1981a).

Animals

Short-term Exposure

- The acute oral toxicity of trifluralin is low. The following oral LD_{50} values have been reported: mice >5 g/kg; rats >10 g/kg; dogs, rabbits and chickens >2 g/kg (Meister, 1983; RTECS, 1985).

- An inhalation LC_{50} value of a liquid formulation containing 41% trifluralin (species not stated) of >2.44 mg/L/hour was reported (U.S. EPA, 1985c). No other information was available.

Dermal/Ocular Effects

- The results of a primary dermal-irritation study in the rabbit were negative at 72 hours following application of a 41.2% trifluralin solution (U.S. EPA, 1985c).

- Treflan, containing 10% trifluralin, was tested for sensitization in female guinea pigs. A dose of 50 mg was applied to the skin of 12 animals, three times a week for 2 weeks. No dermal irritation or contact sensitization developed during this time (Negelski et al., 1984).

- In a similar study, a 95% technical trifluralin solution was shown to be a potential skin sensitizer in guinea pigs using the Buehler topical-patch method (U.S. EPA, 1985c).

- A 14-day study in which rabbits were exposed to 2 ml/kg trifluralin topically produced diarrhea and slight dermal erythema in exposed animals. No other effects were reported (ELANCO, 1979).

- Technical-grade trifluralin applied as a powder to rabbit eyes was reported as nonirritating. Slight conjunctivitis developed but cleared within a week (U.S. EPA, 1985c).

- When applied as a 41.2% liquid to rabbit eyes, trifluralin produced corneal opacity that cleared in 7 days (U.S. EPA, 1985c).

Long-term Exposure

- In a modified subacute study, female Harlan Wistar-derived rats were given 0, 0.05, 0.1 or 0.2% (0, 500, 1,000 or 2,000 ppm) trifluralin in their diet for 3 months. Assuming that 1 ppm in the diet of rats equals 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 25, 50 and 100 mg/kg/day. Physical appearance, behavior, body and organ weights, mortality and clinical chemistries were monitored in progeny from 10 females. No significant effects were observed in survival or appearance. Liver weights in progeny continuously fed diets of 0.1% and 0.2% trifluralin were increased over those of control animals. The study identified a No-Observed-Adverse-Effect Level (NOAEL) in progeny of 0.05% (25 mg/kg) trifluralin (Worth et al., 1977)

- In a 90-day study, male F344 rats were fed trifluralin at dietary levels of 0 (n=60), 0.005% (n=60), 0.02% (n=45), 0.08% (n=45), 0.32% (n=45) and 0.64% (n=45). These concentrations are equivalent to dietary levels of 0, 50, 200, 800, 3,200 and 6,400 ppm trifluralin, respectively (Emmerson et al., 1985). Assuming that 1 ppm in the diet of a rat equals 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of 0, 2.5, 10, 40, 160 and 320 mg/kg/day. After 90 days, alpha-1, alpha-2 and beta-globulin levels were significantly increased in all treatment groups. Other effects included increased aspartate transaminase, urinary calcium, inorganic phosphorus and magnesium at levels ≥160 mg/kg/day. A Lowest-Observed-Adverse-Effect Level (LOAEL) of 2.5 mg/kg/day (the lowest dose tested) can be identified from this study.

- Sixty weanling Harlan rats were fed 0, 20, 200, 2,000 or 20,000 ppm trifluralin in the diet for 729 days (24 months). Assuming that 1 ppm in the diet of a rat equals 0.05 mg/kg (Lehman, 1959), these concentrations correspond to doses of 0, 1, 10, 100 or 1,000 mg/kg/day. No significant effects were observed in growth rate, mortality or food consumption of treated animals at the three lower dose levels. Animals in the highest dose group (1,000 mg/kg/day) were significantly smaller than controls and ranked lower in food consumption. No effects on hematology were noted. Animals in the high-dose group displayed a slight proliferation of the bile ducts. No other histopathological effects were observed. A NOAEL of 2,000 ppm (100 mg/kg/day) was reported (Worth et al., 1966c).

- In a 2-year chronic carcinogenicity study with F344 rats, doses greater than 128 mg/kg/day in males and 154 mg/kg/day in females were reported to produce overt toxicity. Groups of 60 animals/sex/dose were fed dietary levels of 0.08, 0.3 or 0.65% (30, 128 or 272 mg/kg/day for males, and 37, 154 or 336 mg/kg/day for females) trifluralin. Body weights of the high-dose groups were significantly decreased in both sexes. This may be related to the decreased food consumption observed in those groups. Increased blood urea nitrogen (BUN) levels and increased liver and testes weights were noted in the two high-dose groups. Kidney and heart weights were significantly decreased in females in the 0.3- and 0.65%-trifluralin groups. Other noncarcinogenic effects included decreased hemoglobin values and erythrocyte counts in both sexes of the high-dose group (Emmerson and Pierce, 1980). This study appears to identify a NOAEL of 0.08% trifluralin (30 to 37 mg/kg/day).

- B6C3F$_1$ mice (40/sex/group) were exposed to dose levels of 40, 180 or 420 mg/kg/day trifluralin in the diet for 2 years. Animals exposed to the two higher levels exhibited decreased body weight and renal toxicity. Other noncarcinogenic effects included decreased erythrocytic and leukocytic values in the high-dose group, increased BUN and alkaline phosphatase levels in the 180- and 420-mg/kg/day group, decreased kidney weights in the two high-dose groups and decreased spleen and uterine weights with increased liver weights in the high-dose group (Emmerson and Owen, 1980). No effects were noted at the low-dose level (40 mg/kg/day).

- Occasional emesis and increased liver-to-body weight ratios were observed in dogs (three/sex/dose) fed 25 mg/kg/day trifluralin for 3 years. No adverse effects were observed in animals fed 10 mg/kg/day (Worth, 1970). An intermediate dose was not tested.

Reproductive Effects

- In a four-generation reproduction study (Worth et al., 1966b), rats were given 0, 200 or 2,000 ppm trifluralin in the diet (0, 10 or 100 mg/kg/day). A reproductive NOAEL of 200 ppm (10 mg/kg/day) was identified. The number of animals used in the study was not reported. However, a review of this study (U.S. EPA, 1985c) indicated that an insufficient number of animals were used and that several other deficiencies in the study may have compromised the integrity of the results.

- In a 3-year feeding study in dogs a NOAEL of 10 mg/kg/day was identified in adults (Worth et al., 1966b). Dogs (two/sex/dose at 400 ppm and three/sex/dose at 1,000 ppm) were given 10 or 25 mg/kg/day trifluralin in the diet. When bred after 2 years of exposure, no differences in litter size, survival or growth of the pups were reported. An occasional emesis and increased liver weights were reported in adults in the 25-mg/kg/day group.

Developmental Effects

- Female rabbits (number not specified) were fed 0, 100, 225, 500, or 800 mg/kg/day by gavage during pregnancy (ELANCO, 1984). No adverse reproductive effects were observed at the two lower dose levels. The 500 and 800 mg/kg/day levels resulted in anorexia, aborted litters and decreased live births. The NOAEL for maternal effects was identified as 225 mg/kg/day.

- Rabbits (number not specified) exposed to 225 or 500 mg/kg/day trifluralin during pregnancy exhibited anorexia and cachexia and aborted litters (U.S. EPA, 1985c). Fetotoxicity as evidenced by decreased fetal weight and size was observed at the high-dose level. These effects were not observed at the 100 mg/kg/day level.

- In a rabbit teratology study, a total of 32 mated females were given 225, 450 or 1,000 mg/kg/day trifluralin by gavage (Worth et al., 1966a). Animals were dosed until the 25th day of gestation and then sacrificed. Does in the 1,000 mg/kg/day group weighed slightly less than controls. Two fetuses were found to be underdeveloped in the high-dose group; however, this was not considered by the investigators to be treatment related. Average litter size and weight were not significantly affected. The authors reported that their results identified a safe level of 1,000 mg/kg/day.

- Rabbit does (number per group not specified) were given 100, 225, 500 or 800 mg/kg/day trifluralin by gavage during pregnancy (ELANCO, 1984). The 500 and 800 mg/kg/day levels resulted in decreased live births, cardiomegaly and wavy ribs in the progeny. No effects on progeny were observed at 225 mg/kg/day or less (ELANCO, 1984).

Mutagenicity

- Anderson et al. (1972) reported that trifluralin did not induce point mutations in any of the three microbial systems tested. No further details were provided in the review.

- Trifluralin was tested for genotoxicity in several in vivo and in vitro systems (ELANCO, 1983). No reverse mutations were observed in Salmonella typhimurium or Escherichia coli when incubated with 25 to 400 mg trifluralin/plate without activation; trifluralin was also negative when tested at levels of 50 to 800 mg/plate with activation.

Negative results were obtained in mouse lymphoma L5178Y TK$^+$ cells incubated with 0.5 to 20 ug/mL trifluralin with and without activation. An *in vivo* sister-chromatid exchange study in Chinese Hamster Ovary (CHO) cells following exposure to 500 mg/kg trifluralin was also negative.

Carcinogenicity

- NCI (1978) conducted bioassays on B6C3F$_1$ mice and Osborne-Mendel rats using technical-grade trifluralin (which contained 84 to 88 ppm of the contaminant dipropylnitrosamine). Two dietary levels were used in each bioassay. Mice (50/sex/group) were exposed to trifluralin at dose levels of 2,000 or 3,744 ppm (males) or 2,740 or 5,192 ppm (females) for 78 weeks and observed for an additional 13 weeks after exposure. A significant dose-related increase in hepatocellular carcinomas was observed in female mice (0/20 control, 12/47 low dose, 21/44 high dose). An increased incidence of alveolar/ bronchiolar adenomas was also observed (0/19 control, 6/43 low dose, 3/30 high dose) in female mice. Squamous cell carcinomas in the forestomach of a few treated female mice were also observed. Although the incidence of squamous cell carcinomas in the forestomach was not statistically significant when compared to pooled and matched controls, NCI deemed this finding to be treatment related, since it was an unusual type of lesion. Male mice were not significantly affected by trifluralin exposure.

- Rats (50/sex/group) were exposed to two levels of trifluralin in the feed (4,125 or 8,000 ppm for males; 4,125 or 7,917 ppm for females) for 78 weeks followed by a 33-week observation period (NCI, 1978). Assuming 1 ppm in the diet of rats equals 0.05 mg/kg/day (Lehman, 1959), these doses correspond to approximately 206 or 400 mg/kg/day. Several neoplasms were observed and compared to pooled and matched controls. These neoplasm types were reported to occur spontaneously in the Osborne-Mendel strain and were not considered treatment related by NCI.

- In a 2-year feeding study, B6C3F$_1$ mice were given 0, 563, 2,250 or 4,500 ppm trifluralin (assuming 1 ppm in the diet of a mouse equals 0.15 mg/kg/day, these doses correspond to 40, 180 or 420 mg/kg/day (Lehman, 1959) in the diet (Emmerson and Owen, 1980). Levels of a nitrosamine contaminant of trifluralin, NDPA, were below the 0.01-ppm analytical detection limit. A total of 40 animals/sex/treatment group was used and 60/sex for controls. At the lowest dose level, 40 mg/kg/day, no adverse effects were observed in either sex. Decreased body weight and renal effects were noted in mice in the mid- and high-dose groups. Pathology revealed progressive glomerulonephritis in females of the high-dose group. Hepatocellular hyperplasia and hypertrophy were also observed in the treated mice. The specific dose level was not reported. No evidence of increased incidence or decreased latency for any type of neoplasm was found in any of the mice.

- Trifluralin was administered to F344 rats (60/sex/group) at dose levels of 813, 3,250 or 6,500 ppm; (corresponding to 30, 128 or 272 mg/kg/day for males and 37, 154 or 336 mg/kg/day for females) in the diet for 2 years (Emmerson and Pierce, 1980). A significant increase in malignant renal neoplasms and thyroid tumors in male rats and in neoplasms of the bladder in both sexes was reported. A high incidence (20/30) of renal calculi was also observed in animals in the high-dose groups.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L}\ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for trifluralin. Therefore, it is recommended that a modified DWEL (0.03 mg/L, calculated below) for a 10-kg child be used as a conservative estimate for the One-day HA value.

For a 10-kg child, the adjusted DWEL is calculated as follows:

$$\text{DWEL} = \frac{(0.0025\ \text{mg/kg/day})\ (10\ \text{kg})}{1\ \text{L/day}} = 0.025\ \text{mg/L}\ (30\ \text{ug/l})$$

where:

0.0025 mg/kg/day = Rfd (see Lifetime Health Advisory Section).

10 kg = assumed body weight of a child.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

No information was found in the available literature that was suitable for determination of the Ten-day HA value for trifluralin. It is, therefore, recommended that a modified DWEL (0.03 mg/L) for a 10-kg child be used as a conservative estimate for the Ten-day HA value.

Longer-term Health Advisory

No information was found in the available literature that was suitable for determination of the Longer-term HA value for trifluralin. It is, therefore, recommended that a modified DWEL (0.03 mg/L) for a 10-kg child be used as a conservative estimate for a Longer-term exposure for a child and the DWEL (0.1 mg/L; calculated below) be used for the adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The Emmerson et al. (1985) study has been selected to serve as the basis for the Lifetime HA value for trifluralin. F344 rats were fed diets containing 0.005, 0.02, 0.08, 0.32 or 0.64% trifluralin (2.5, 10, 40, 160 or 320 mg/kg/day) for 90 days. Significant increases in urinary alpha-1, alpha-2, and beta-globulins were observed in all treated animals. A NOAEL was not identified. Other longer-term studies report NOAELs at higher doses.

Using a LOAEL of 2.5 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(2.5 \text{ mg/kg/day})}{(1,000)} = 0.0025 \text{ mg/kg/day } (0.003 \text{ mg/kg/day})$$

where:

2.5 mg/kg/day = LOAEL, based on increased urinary globulins in rats consuming a trifluralin diet for 3 months.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.003\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.105\ \text{mg/L}\ (100\ \text{ug/L})$$

where:

0.0025 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(0.105\ \text{mg/L})\ (20\%)}{10} = 0.0021\ \text{mg/L}\ (2\ \text{ug/L})$$

where:

0.105 mg/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), trifluralin may be classified in Group C: possible human carcinogen. This category is used for substances that show limited evidence of carcinogenicity in animals and inadequate evidence in humans.

- In an NCI (1978) study of female B6C3F$_1$ mice, significant dose-related increases in hepatocellular carcinomas and alveolar adenomas were observed when the animals were exposed to 33 or 62 mg/kg/day trifluralin in the diet for 78 weeks. The trifluralin used in this study contained 84 to 88 ppm dipropylnitrosamine. Male rats, when exposed to 30, 128 or 272 mg/kg/day trifluralin in the diet for 2 years, exhibited significant increases in the incidences of kidney, urinary bladder and thyroid tumors (Emmerson and Pierce, 1980).

- The evidence from the Emmerson and Pierce (1980) and NCI (1978) studies indicates that trifluralin has carcinogenic potential. Based on the results of the Emmerson and Pierce (1980) study, the U.S. EPA Carcinogen Assessment Group (CAG) has prepared a quantitative risk estimate of trifluralin exposure (U.S. EPA, 1981b). The CAG estimated a potency factor (q_1*) of 7.66 x 10^{-3} mg/kg/day based on the combined incidence of tumors in male rats. Assuming that a 70-kg human adult consumes 2 liters of water per day over a 70-year lifespan, the estimated cancer risk would be 10^{-4}, 10^{-5} and 10^{-6} at concentrations of 500, 50 and 5 ug/L, respectively.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Residue tolerances ranging from 0.05 to 2.0 ppm trifluralin have been established for a variety of agricultural commodities (U.S. EPA, 1985).
- NAS (1977) has calculated an ADI of 0.1 mg/kg bw/day with a Suggested-No-Adverse-Response-Level (SNARL) of 700 ug/L.

VII. ANALYTICAL METHODS

- Determination of trifluralin is by Method 508 (U.S. EPA, 1987). In this procedure, a measured volume of sample of approximately 1 liter is solvent-extracted with methylene chloride by mechanical shaking in a separatory funnel or mechanical tumbling in a bottle. The methylene chloride extract is isolated, dried and concentrated to a volume of 5 mL after solvent substitution with methyl tert-butyl ether (MTBE). Chromatographic conditions are described which permit the separation and measurement of the analytes in the extract by GC with an electron capture detector (ECD). An alternative manual liquid-liquid extraction method using separatory funnels is also described. This method has been validated in a single laboratory, and the estimated detection limit determined for the analytes in this method, including trifluralin, is 0.025 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that reverse osmosis (RO), granular-activated carbon (GAC) adsorption conventional treatment and possibly air stripping will remove trifluralin from water.
- U.S. EPA investigated the amenability of a number of compounds, including trifluralin, to removal by GAC. No system performance data were given.
- Conventional water treatment techniques of coagulation with alum, sedimentation and filtration proved to be 100% effective in removing trifluralin from contaminated water (Nye, 1984).

- Sanders and Seibert (1983) determined experimentally water solubility, vapor pressure, Henry's Law Constant and volatilization rates for trifluralin; 100% of the compound volatilized under laboratory conditions.

- Treatment technologies for the removal of trifluralin from water are available and have been reported to be effective. However, selection of individual technology or combination of technologies to attempt trifluralin removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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